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(54) **SOLUBILITY PARAMETER BASED DRUG DELIVERY SYSTEM AND METHOD FOR ALTERING DRUG SATURATION CONCENTRATION**

AUF EINEM LÖSLICHKEITSPARAMETER BASIERENDES MEDIKAMENTENABGABESYSTEM SOWIE VERFAHREN ZUR ÄNDERUNG DER SÄTTIGUNGSKONZENTRATION EINES MEDIKAMENTS

SYSTEME D'APPORT DE MEDICAMENTS FONDE SUR UN PARAMETRE DE SOLUBILITE ET PROCEDE MODIFIANT LA CONCENTRATION DE SATURATION D'UN MEDICAMENT

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(73) Proprietor: **NOVEN PHARMACEUTICALS, INC.**
Miami, FL 33186 (US)

(72) Inventors:
- **MIRANDA, Jesus**
  Miami, FL 33186 (US)
- **SABLOTSKY, Steven**
  Miami, FL 33176 (US)

(74) Representative:
Werner, Hans-Karsten, Dr.Dipl.-Chem. et al
Patentanwälte
von Kreisler-Selting-Werner,
Deichmannhaus (Bahnhofsvorplatz)
50667 Köln (DE)

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Description

Background of the Invention

[0001] This invention relates generally to transdermal drug delivery systems, and more particularly, to a transdermal drug delivery composition wherein a blend of polymers is utilized to affect the rate of drug delivery from the composition. More specifically, a plurality of polymers having differing solubility parameters, preferably immiscible with each other, adjusts the solubility of the drug in a polymeric adhesive system formed by the blend and modulates the delivery of the drug from the composition and through the dermis.

[0002] The use of a transdermal composition, for example a pressure-sensitive adhesive containing a medicament, namely, a drug, as a means of controlling drug delivery through the skin at essentially a constant rate, is well known. Such known delivery systems involve incorporation of a medicament into a carrier such as a polymeric matrix and/or a pressure-sensitive adhesive formulation. The pressure-sensitive adhesive must adhere effectively to the skin and permit migration of the medicament from the carrier through the skin and into the bloodstream of the patient.

[0003] Many factors influence the design and performance of sustained or controlled release drug delivery products, and dermal delivery systems in general, including drug properties, optimum delivery rate, target site(s), type of therapy (short-term or chronic), patient compliance, *etc.* Among the drug properties which are known to influence the rate of release or permeation, or both, into the skin are the physicochemical properties, including molecular size, shape, and volume; solubility (both in the delivery system and through the skin); partitioning characteristics; degree of ionization; charge; and protein binding propensity.

[0004] When a drug is contained in a carrier, for example, a pressure-sensitive adhesive for transdermal delivery, the rate of administration may be affected by the rate of release of the drug from the carrier, as well as the rate of passage of the drug through the skin. These rates vary from drug-to-drug and from carrier-to-carrier. A variety of mathematical equations have been proposed in the prior art to describe theoretically the fundamentals of mass transfer phenomena involved in diffusion through a carrier and development of a flux across a membrane such as the skin.

[0005] Transdermal drug delivery systems can be divided into two general groups: system-controlled and skin-controlled devices. With skin-controlled devices, net drug delivery is controlled by the rate of drug permeation through the skin. Skin-controlled systems can be further subdivided into monolithic devices and reservoir devices.

[0006] Generally, a monolithic system comprises a drug dispersed or dissolved in a matrix comprising a homogeneous polymeric material of, illustratively, silicone adhesive, silicone rubber, acrylic adhesive, polyethylene, polyisobutylene, polyvinyl chloride, nylon, or the like. The drug is dissolved in the polymeric matrix until its saturation concentration is reached. Any additional drug remains dispersed within the matrix. As drug is removed from the surface of the matrix, more of the drug diffuses out of the interior in response to the decreased concentration at the surface. The release rate is therefore not constant over time, but instead gradually decreases as the drug concentration decreases.

[0007] The flux, or percutaneous absorption rate of drugs through the skin, is described by Fick's first law of diffusion:

$$J = -D(dC_m/dx),$$

where J is the flux in $g/cm^2/sec$, D is the diffusion coefficient of the drug through the skin in cm^2/sec, and dC_m/dx is the concentration gradient of active agent across the skin.

[0008] In order to modify the rate of delivery from a monolithic transdermal device and into the dermis, the prior art has typically focused on selecting a specific single-polymer matrix or a blend of soluble (miscible) polymers. Illustrative examples are the novel polymers described in U.S. Patent Nos. 4,898,920 and U.S. 4,751,087. There is a need in the art to modify the rate of delivery while using commercially available polymer components.

[0009] EP-A-0 312 265 discloses adhesive compositions comprising blends of polyethylene oxide-grafted silicone polymers with resinous copolymers. The adhesive compositions enhance release, in a controlled fashion, of bioactive or chemical agents blended or ortherwise dispersed through the compositions. Transdermal drug delivery devices incorporating the adhesive compositions are also disclosed.

[0010] Another common technique for modifying the rate of drug delivery is the addition of a vehicle or enhancer to the formulation to increase the solubility of the drug within the polymer matrix, for example by adding a co-solvent such as a polyhydric alcohol or by changing the skin permeability, for example by adding enhancers such as ethanol. There is a further need to be able to modulate the delivery of a drug from a polymer matrix without adding vehicles or enhancers.

[0011] There is no example in the prior art of using a simple blend of adhesive polymers to affect the rate of drug delivery from a monolithic adhesive-based transdermal composition. However, U.S. Patent No. 4,814,168, granted March 21, 1989, and a continuation-in-part thereof, U.S. Patent No. 4,994,267, issued on February 19, 1991, both assigned to Noven Pharmaceuticals, Inc., Miami, FL, disclose the use of a multipolymer, specifically an ethylene/vinyl

acetate copolymer or an ethylene/vinyl acetate/acrylic terpolymer, a rubber and a tackifier in a carrier composition to improve the adhesive properties. The composition of U.S. Patent No. 4,994,267 further includes an acrylate polymer in the system for additional improvement to the adhesive properties.

[0012] Drug concentration in a monolithic transdermal delivery device can vary widely depending on the drug and polymers used. For example, certain drugs are effective in low doses and therefore the transdermal formulation may involve low concentrations, illustratively 5% or less by weight of the medicament in an adhesive. Other drugs, such as nitroglycerin, require large doses to be effective and the transdermal formulation therefore may involve high drug concentrations, approximately between 5 to 40% or more by weight in an adhesive. Low concentrations of medicament typically do not critically affect the adhesion, tack, and shear resistance properties of the adhesive. However, low drug concentrations in the adhesive can result in difficulties in achieving an acceptable delivery rate of the medicament. High concentrations, on the other hand, frequently affect the adhesion properties of the adhesives. The deleterious effects are particularly exacerbated by drugs which also act as plasticizersor solvents for the polymeric adhesive material (*e.g.*, nitroglycerin in polyacrylates).

[0013] There is a need in the art for an adhesive composition for transdermal delivery systems which can selectably incorporate low concentrations of drug and deliver same at an adequate and controlled rate or incorporate high concentrations of drugs while retaining good physical adhesive properties.

[0014] It is, therefore, an object of this invention to provide a transdermal drug delivery system wherein the rate of drug delivery from the transdermal composition may be selectably modulated.

[0015] It is another object of this invention to provide a transdermal drug delivery system wherein the rate of drug delivery from the transdermal composition may be selectably modulated by adjusting the solubility and/or diffusivity of the drug in the multiple polymer adhesive system.

[0016] It is also an object of this invention to provide a transdermal drug delivery system wherein the multiple polymer adhesive system is simple to manufacture.

[0017] It is a further object of this invention to provide a transdermal drug delivery system wherein drug-loading of a multiple polymer adhesive system may be selectably varied without adverse effects on drug delivery rate and adhesive properties, such as adhesion, tack, and shear resistance.

[0018] It is additionally an object of this invention to provide a transdermal drug delivery system wherein a novel multiple polymer adhesive system is provided which has desirable physical properties.

Summary of Invention

[0019] The foregoing and other objects are achieved by this invention which provides a transdermal drug delivery system as defined in claim 1 and a method of modulating the delivery rate of a drug as defined in claim 59.

[0020] In accordance with a composition aspect of the invention, an improved pressure-sensitive adhesive composition of the type which is suitable as a matrix for controlled release of a bioactive agent therefrom comprises a blend of a first polymeric adhesive material having a first solubility parameter and a second polymeric adhesive material having a second solubility parameter, the first and second solubility parameters being different from one another. The blend, therefore, has a characteristic net solubility parameter. In embodiments incorporating a bioactive agent in the improved pressure-sensitive adhesive composition, the characteristic net solubility parameter can be preselected to adjust the saturation concentration of a bioactive agent in the composition and thereby control the release of the bioactive agent. The saturation concentration of the bioactive agent may be adjusted either upward or downward depending upon whether the rate of release is to be enhanced or retarded.

[0021] The bioactive agent comprises a drug. In preferred embodiments, the drug is a steroid, such as an estrogen or a progestational agent, or combination thereof. In other preferred embodiments, the drug may be a β_2-adrenergic agonist, such as albuterol, or a cardioactive agent, such as nitroglycerin. In still other embodiments, the bioactive agent is a cholinergic agent, such as pilocarpine, or an antipsychotic such as haloperidol or a tranquilizer/sedative such as alprazolam.

[0022] The pressure-sensitive adhesive composition may further include enhancers, fillers, co-solvents, and excipients as are known in the art for use in such compositions.

[0023] In the improved pressure-sensitive adhesive, the first polymeric adhesive material is a polyacrylate and the second adhesive material is a polysiloxane or a hydrocarbonpolymer. The polyacrylate is preferably present in the pressure-sensitive adhesive composition in an amount ranging from about 2-96% by weight and the polysiloxane is present in an amount ranging from about 98-4%. Preferably, the ratio of polyacrylate to polysiloxane is from about 2:98 to about 96:4, and more preferably from about 2:98 to about 86:14 by weight.

[0024] In a dermal adhesive composition embodiment of the invention, a multiple polymer adhesive system consisting essentially of a blend of 2-96% by weight of an acrylate polymer and 98-4% by weight of a polymer of siloxane, the multiple polymer adhesive system being in an amount of about 99-50% by weight of the dermal adhesive composition. This is combined with a bioactive agent in the amount of 0.3-50% by weight of the total dermal adhesive composition.

Optional additives, such as co-solvent for the bioactive agent (up to 30% by weight) and enhancers (up to 20% by weight) may be included in the dermal adhesive composition.

[0025] In a transdermal drug delivery device embodiment, the improved pressure-sensitive adhesive of the present invention is combined with a drug. The transdermal drug delivery device may comprise a monolithic adhesive matrix device in some embodiments. Of course, the transdermal drug delivery device may include a backing material and a release liner as is known in the art.

[0026] The saturation concentration of a drug in a transdermal drug delivery device of the type having a drug-containing pressure-sensitive adhesive diffusion matrix is adjusted in accordance with a method aspect of the present invention by blending at least two polymers having differing solubility parameters to form a pressure-sensitive adhesive diffusion matrix having a net solubility parameter which modifies the delivery rate of the a drug from the pressure-sensitive adhesive diffusion matrix and through the dermis.

Brief Description of the Drawing

[0027] Comprehension of the invention is facilitated by reading the following detailed description, in conjunction with the annexed drawing, in which:

FIG. 1 is a schematic illustration of a monolithic transdermal drug delivery device of the present invention;

FIG. 2 is a graphic representation of the steady-state nitroglycerin flux rates through cadaver skin *in vitro* from a transdermal drug delivery composition of the present invention (formulation of Example 1) and two commercially-available nitroglycerin-containing transdermal delivery devices: Transderm-Nitro® (a trademark of Ciba-Geigy Corporation, Summit, NJ), and Nitro-Dur® (a trademark of Key Pharmaceuticals, Inc., Kenilworth, NJ);

FIG. 3 is a graphical representation which summarizes *in vitro* nitroglycerin flux results through cadaver skin for the polymeric systems of Examples 2-5. The composition of Example 2 (polyacrylate-only adhesive) is compared to the multiple polymer compositions of Examples 3, 4, and 5, in which the polyacrylate is blended with a polyethylene vinyl acetate, a polyisobutylene, and a polysiloxane, respectively;

FIG. 4 is a graphical representation of the steady-state nitroglycerin flux through cadaver skin *in vitro* from a multiple polymer transdermal adhesive system of Example 6 comprising various weight ratios of polyacrylate and polysiloxane;

FIG. 5 is a graphical representation of steady-state estradiol flux through cadaver skin *in vitro* from the drug delivery systems of the prior art, specifically single polymeric adhesives of silicone and acrylic, as compared to a multiple polymer transdermal adhesive system (polyacrylate/polysiloxane) of the present invention;

FIG. 6 is a graphical representation of average estradiol flux through cadaver skin *in vitro* from 0 to 22 hours and from 22 to 99 hours for a multiple polymer transdermal adhesive system comprising various weight ratios of polyacrylate and polysiloxane;

FIG. 7 is a graphical representation of steady-state norethindrone acetate flux through cadaver skin *in vitro* from the drug delivery systems of the prior art, specifically single polymeric adhesives of silicone and acrylic, as compared to a multiple polymer transdermal adhesive system (polyacrylate/polysiloxane) of the present invention;

FIG. 8 is a graphical representation of average estradiol and norethindrone acetate flux through cadaver skin *in vitro* for a multiple polymer transdermal adhesive system comprising both drugs and various weight ratios of polyacrylate and polysiloxane;

FIG. 9 is a graphical representation showing the ratio of average estradiol to norethindrone acetate flux (estradiol flux divided by norethindrone acetate flux) through cadaver skin *in vitro* for a multiple polymer transdermal adhesive system comprising various weight ratios of polyacrylate and polysiloxane;

FIG. 10 is a graphical representation of steady-state flux of pilocarpine through cadaver skin *in vitro* from the drug delivery systems of the prior art, specifically single polymeric adhesives of silicone and acrylic, as compared to a multiple polymer transdermal adhesive system (polyacrylate/polysiloxane) of the present invention;

FIG. 11 is a graphical representation of steady-state albuterol and nitroglycerin flux through cadaver skin *in vitro* from multiple polymer transdermal adhesive systems (polyacrylate/polysiloxane) of the present invention (Examples 24 - 27), and Nitro-Dur®, respectively;

FIG. 12 is a graphical representation of steady-state estradiol flux through cadaver skin *in vitro* from two different multiple polymer transdermal adhesive systems polyacrylate/ polysiloxane and polyacrylate/polybutylene;

FIGS. 13 and 14 show the relationship of flux rate (J) plotted against apparent diffusion coefficient (D) and net solubility parameter (SP), respectively, for Compositions I-VI of Example 6. The net solubility parameter, SP_{net}, was calculated using a weighted average of the solubility parameters of the individual polymers comprising the matrix:

$$SP_{net} = \varnothing_{ps} SP_{ps} + \varnothing_{pa} SP_{pa},$$

where $\varnothing_{ps}$ is the weight percentage of polysiloxane and SP_{ps} is the solubility parameter of polysiloxane. The subscript "pa" refers to the polyacrylate; and

FIG. 15 is a plot of diffusion coefficient versus net solubility parameter.

Detailed Description

[0028] In one aspect of the present invention, a pressure-sensitive adhesive composition is provided which comprises a blend of at least two polymers. The blend of at least two polymers is herein referred to as a multiple polymer adhesive system. The term "blend" is used herein to mean that there is no, or substantially no, chemical reaction or cross-linking (other than simple H-bonding) between the polymers in the multiple polymer adhesive system.

[0029] In another aspect of the invention, a controlled release dermal composition comprises a drug, or other bioactive agent, in combination with the multiple polymer adhesive system. In this aspect, the multiple polymer adhesive not only functions as a carrier matrix for the drug, but enhances the rate of release of the drug, and hence the transdermal permeation rate. In some embodiments of the invention, however, the multiple polymer adhesive system will function to retard the transdermal permeation rate.

[0030] The invention is premised on the discovery that the transdermal permeation rate of a drug from the multiple polymer adhesive system can be selectively modulated by adjusting the solubility of the drug in the device. As used herein, the term "transdermal permeation rate" means the rate of passage of the drug through the skin; which, as known in the art, may or may not be affected by the rate of release of the drug from the carrier.

[0031] The polymers comprising the multiple polymer adhesive system are inert to the drug, and are preferably immiscible with each other. Forming a blend of multiple polymers results in an adhesive system having a characteristic "net solubility parameter," the selection of which advantageously permits a selectable modulation of the delivery rate of the drug by adjusting the solubility of the drug in the multiple polymer adhesive system.

[0032] Solubility parameter, also referred to herein as "SP", has been defined as the sum of all the intermolecular attractive forces, which are empirically related to the extent of mutual solubility of many chemical species. A general discussion of solubility parameters is found in an article by Vaughan, "Using Solubility Parameters in Cosmetics Formulation," J. Soc. Cosmet. Chem., Vol.36, pages 319-333 (1985). Many methods have been developed for the determination of solubility parameters, ranging from theoretical calculations to totally empirical correlations. The most convenient method is Hildebrand's method, which computes the solubility parameter from molecular weight, boiling point and density data, which are commonly available for many materials and which yields values which are usually within the range of other methods of calculation:

$$SP = (\Delta E_v / V)^{1/2},$$

where V = molecular weight/density and ΔE_v = energy of vaporization.

[0033] Alternatively written, $SP = (\Delta H_v / V - RT/V)^{1/2}$

where ΔH_v = heat of vaporization, R = gas constant, and T is the absolute temperature, °K. For materials, such as high molecular weight polymers, which have vapor pressures too low to detect, and thus for which ΔH_v is not available, several methods have been developed which use the summation of atomic and group contributions to ΔH_v:

$$\Delta Hv = \Sigma_i \Delta h_i,$$

where Δh_i is the contribution of the ith atom or group to the molar heat of vaporization. One convenient method has been proposed by R. F. Fedors, Polymer Engineering and Science, Vol. 14, p. 147 (1974). In this method ΔE_v and V are be obtained by simply assuming that

$\Delta Ev = \Sigma_i \Delta e_i$ and $V = \Sigma_i v_i$, where Δe_i and v_i are the additive atomic and group contributions for the energy of vaporization and molar volume, respectively.

[0034] Yet another method of calculating the solubility parameter of a material is described by Small, J. Applied Chem. Vol. 3, p. 71 (1953).

[0035] Table I-A below sets forth solubility parameters of some exemplary adhesive polymers which would be useful in the practice of the invention and shows the variation of SP with molecular weight, free -OH and -COOH groups, the degree of cross-linking. Table IA is in $(cal/cm^3)^{1/2}$ and $(J/cm^3)^{1/2}$ as calculated by Small's method.

TABLE IA

Polymers	Solubility Parameter	
Addition polymers of unsaturated esters	$(cal/cm^3)^{1/2}$	$(J/cm^3)^{1/2}$
Polymethyl methacrylate	9.3	19.0
Polyethylmethacrylate	9.1	18.6
Polymethylacrylate	9.7	19.8
Polyethylacrylate	9.2	18.8
Hydrocarbon polymers		
Polyethylene	8.1	16.6
Polystyrene	9.1	18.6
Polyisobutylene	7.7	15.7
Polyisoprene	8.1	16.6
Polybutadiene	8.4	16.6
Polyethylene/butylene	7.9	16.2
Halogen-containing polymers		
Polytetrafluoroethylene	6.2	12.7
Polyvinylchloride	9.5	19.4
Polyvinylidene chloride	12.2	24.9
Polychloroprene	9.4	19.2
Polyacrylonitrile	12.7	26.0
Condensation polymers		
Nylon -6.6	13.6	27.8
Epon resin 1004 (epoxy)	9.7	19.8
Polysiloxanes		
Polydimethylsiloxane	7.3	14.9
Copolymers		
Polybutadiene-co-acrylonitrile: 75/25 to 70/30	9.25	18.9
Polybutadiene-co-styrene: 75/25 to 72/28	8.5	17.4
excerpted from Kraton® Thermoplastic Rubber Shell Chemical Co. Product Brochure Number SC: 198-89		

[0036] Table I-B below sets forth solubility parameters calculated by Fedors' method and are expressed in units of $(J/cm^3)^{1/2}$.

TABLE I-B

Components	Solubility Parameter, $(J/cm^3)^{1/2}$
polyethylene/vinyl acetate (40% VAc)	20.9
polydimethylsiloxane	15.1
polyisobutylene	17.6
polyethylene	17.6
polyethyl methacrylate	19.8
polyethyl acrylate	20.9
polymethyl acrylate	21.7
polymethyl methacrylate	22.3
polystyrene	22.5

TABLE I-B (continued)

Components	Solubility Parameter, $(J/cm^3)^{1/2}$
nitroglycerin	27.0
estradiol	24.5
norethindrone acetate	21.3
pilocarpine	22.9
albuterol	26.7

[0037] In accordance with the principles of the invention, the transdermal permeation rate is controlled by varying the polymer components of the multiple polymer adhesive system so as to alter the difference in the solubility parameter of the multiple polymer adhesive system relative to that of the drug (see Examples 2-5, or 28 and 29, hereinbelow). Preferably the solubility parameters of the polymer components are different from one another by an increment of at least 2 $(J/cm^3)^{1/2}$. Most preferably they differ by at least 4 $(J/cm^3)^{1/2}$.

[0038] The transdermal permeation rate is also controlled by varying the relative proportions of the polymers comprising the multiple polymer adhesive system (see Example 6 hereinbelow).

[0039] The multiple polymer adhesive system is preferably formulated so that it is a pressure-sensitive adhesive at room temperature and has other desirable characteristics for adhesives used in the transdermal drug delivery art; such characteristics include good adherence to skin, ability to be peeled or otherwise removed without substantial trauma to the skin, retention of tack with aging, *etc.* In general, the multiple polymer adhesive system should have a glass transition temperature (T_g), measured using a differential scanning calorimeter, of between about -70° C to 0° C.

[0040] Selection of the particular polymer composition is governed in large part by the drug to be incorporated in the device, as well as the desired rate of delivery of the drug. Those skilled in the art can readily determine the rate of delivery of drugs from the multiple polymer transdermal adhesive system in order to select suitable combinations of polymers and drug for a particular application. Various techniques can be used to determine the rate of delivery of the drug from the polymer. Illustratively, the rate of delivery can be determined by measuring the transfer of drug from one chamber to another through cadaver skin over time, and calculating, from the obtained data, the drug delivery or flux rate.

[0041] In a particularly preferred embodiment of the invention, the multiple polymer adhesive system comprises a blend of an acrylic pressure-sensitive adhesive and a silicone pressure-sensitive adhesive. The acrylic-based polymer and silicone-based polymer are preferably in a ratio by weight, respectively, from about 2:98 to about 96:4, more preferably from about 2:98 to about 90:10, and even more preferably about 2:98 to about 86:14. The amount of acrylic-based polymer (hereinafter referred to broadly as a polyacrylate) and silicone-based polymer (hereinafter referred to broadly as a polysiloxane) is selected to modify the saturation concentration of the drug in the multiple polymer adhesive system in order to affect the rate of delivery of the drug from the system and through the skin.

[0042] The adjustment to the saturation concentration of the drug in the multiple polymer adhesive system can either be an increase or a decrease. It has been found that when a polyacrylate having a solubility parameter SP of about 21 $(J/cm^3)^{1/2}$ is used as the principal polymer of a nitroglycerin (SP about 27 $(J/cm^3)^{1/2}$) monolithic system, a significant increase in the transdermal permeation rate of nitroglycerin can be achieved by the addition of a polymer having a lower solubility parameter, for example a polysiloxane (SP about 15 $(J/cm^3)^{1/2}$). By reducing the "net" solubility parameter of the multiple polymer transdermal adhesive system, the difference between the solubility parameter of nitroglycerin and the multiple polymer adhesive system is increased. This increased solubility parameter difference, results in a lower saturation concentration for nitroglycerin, and thereby a greater thermodynamic driving force. Conversely, the composition of the multiple polymer adhesive system can be selected so that the saturation concentration of the drug in the system is increased, so the rate of delivery is retarded, such as would be desirable for administration of scopolamine.

[0043] Advantageously, the method and composition of the present invention permit selectable loading of the drug in the transdermal drug delivery system. The concentration by weight of the drug in the dermal composition is preferably about 0.3 to about 50 percent, more preferably about 0.5 to about 40 percent, and even more preferably about 1.0 to about 30 percent. Irrespective of whether there is high-loading or low-loading of the drug into the dermal composition, the multiple polymer adhesive system of the present invention can be formulated to maintain acceptable shear, tack, and peel adhesive properties.

[0044] Although not wishing to be bound by theory, particularly in this case where the structure of the composition has not been analyzed, it is postulated that the polymers of varying solubility parameters, for example, the polysiloxane and the polyacrylate, result in a heterogenous mix, with the components of the polymeric mixture performing as a mutually interpenetrating polymeric network in the composition. In other words, the multiple polymer adhesive system is a mixture of essentially mutually insoluble or immiscible polymers, in contradistinction to the typical prior art transder-

mal drug delivery systems derived from a single polymer or a solution of mutually soluble polymers.

[0045] In the practice of the preferred embodiment of the invention, the acrylic-based polymer can be any of the homopolymers, copolymers, terpolymers, and the like of various acrylic acids. In such preferred embodiments, the acrylic-based polymer constitutes preferably from about 2% to about 95% of the total weight of the total dermal composition, and preferably about 2% to about 90%, and more preferably about 2% to about 85%, the amount of acrylate polymer being dependent on the amount and type of drug used.

[0046] The acrylate polymers of this invention are polymers of one or more monomers of acrylic acids and other copolymerizable monomers. The acrylate polymers also include copolymers of alkyl acrylates and/or methacrylates and/or copolymerizable secondary monomers or monomers with functional groups. By varying the amount of each type of monomer added, the cohesive properties of the resulting acrylate polymer can be changed as is known in the art. In general, the acrylate polymer is composed of at least 50% by weight of an acrylate or alkyl acrylate monomer, from 0 to 20% of a functional monomer copolymerizable with the acrylate, and from 0 to 40% of other monomers.

[0047] Acrylate monomers which can be used include acrylic acid, methacrylic acid, butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, 2-ethylbutyl acrylate, 2-ethylbutyl methacrylate, isooctyl acrylate, isooctyl methacrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate, and tridecyl methacrylate.

[0048] Functional monomers, copolymerizable with the above alkyl acrylates or methacrylates, which can be used include acrylic acid, methacrylic acid, maleic acid, maleic anhydride, hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamide, dimethylacrylamide, acrylonitrile, dimethylaminoethyl acrylate, dimethylaminoethyl methacrylate, tert-butylaminoethyl acrylate, tert-butylaminoethyl methacrylate, methoxyethyl acrylate and methoxyethyl methacrylate.

[0049] Further details and examples of acrylic adhesives which are suitable in the practice of the invention are described in Satas, "Acrylic Adhesives," Handbook of Pressure-Sensitive Adhesive Technology, 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

[0050] Suitable acrylic adhesives are commercially available and include the polyacrylate adhesives sold under the trademarks Duro-Tak 80-1194, Duro-Tak 80-1196, and Duro-Tak 80-1197 by National Starch and Chemical Corporation, Bridgewater, New Jersey.

[0051] Suitable polysiloxanes include silicone pressure-sensitive adhesives which are based on two major components: a polymer, or gum, and a tackifying resin. The polysiloxane adhesive is usually prepared by cross-linking the gum, typically a high molecular weight polydiorganosiloxane, with the resin, to produce a three-dimensional silicate structure, via a condensation reaction in an appropriate organic solvent. The ratio of resin to polymer is the most important factor which can be adjusted in order to modify the physical properties of polysiloxane adhesives. Sobieski, *et al.*, "Silicone Pressure Sensitive Adhesives," Handbook of Pressure-Sensitive Adhesive Technology, 2nd ed., pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

[0052] Further details and examples of silicone pressure sensitive adhesives which are useful in the practice of this invention are described in the following U.S. Patents: 4,591,622; 4,584,355; 4,585,836; and 4,655,767.

[0053] Suitable silicone pressure-sensitive adhesives are commercially available and include the silicone adhesives sold under the trademarks BIO-PSA X7-3027, BIO-PSA X7-4919, BIO-PSA X7-2685, and BIO-PSA X7-3122 by Dow Corning Corporation, Medical Products, Midland, Michigan. BIO-PSA-3027 is particularly suitable for use in formulations containing amine-functional drugs, such as albuterol.

[0054] In the practice of a preferred embodiment of the invention, the polysiloxane constitutes preferably from about 4% to about 97% of the total weight of the total dermal composition, and preferably about 8% to about 97%, and more preferably about 14% to about 97%.

[0055] In practicing the invention, any bioactive agent may be included in the dermal composition. Illustratively the bioactive agent is a drug. Any drug which is capable of producing a pharmacological response, localized or systemic, irrespective of whether therapeutic, diagnostic, or prophylactic in nature, in plants or animals is within the contemplation of the invention. In addition to drugs, bioactive agents such as pesticides, insect repellents, sun screens, cosmetic agents, *etc.* are within the contemplation of the invention. It should be noted that the bioactive agents may be used singly or as a mixture of two or more such agents, and in amounts sufficient to prevent, cure, diagnose or treat a disease, as the case may be.

[0056] Exemplary active drugs that can be administered by the novel transdermal drug delivery system of this invention include, but are not limited to:

1. Cardioactive medications, illustratively, organic nitrates such as nitroglycerin, isosorbide dinitrate, and isosorbide mononitrates; quinidine sulfate; procainamide; thiazides such as bendroflumethiazide, chlorothiazide, and hydrochlorothyazide; nifedipine; nicardipine; adrenergic blocking agents, such as timolol and propranolol; verapamil; diltiazem; captopril; clonidine and prazosin.
2. Androgenic steroids, such as testosterone, methyltestosterone and fluoxymesterone.
3. Estrogens, such as conjugated estrogens, esterified estrogens, estropipate, 17β estradiol, 17β-estradiol valer-

ate, equilin, mestranol, estrone, estriol, 17β-ethinyl estradiol, and diethylstilbestrol.

4. Progestational agents, such as progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, and megestrol acetate.

5. Drugs having an action on the central nervous system, for example sedatives, hyponotics, antianxiety agents, analgesics and anesthetics, such as chloral, buprenorphine, naloxone, haloperidol, fluphenazine, pentobarbital, phenobarbital, secobarbital, codeine, lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine, benzocaine, fentanyl, and nicotine.

6. Nutritional agents, such as vitamins, essential amino acids and essential fats.

7. Anti-inflammatory agents, such as hydrocortisone, cortisone, dexamethasone, fluocinolone, triamcinolone, medrysone, prednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, fludrocortisone, corticosterone, paramethasone, betamethasone, ibuprophen, naproxen, fenoprofen, fenbufen, flurbiprofen, indoprofen, ketoprofen, suprofen, indomethacin, piroxicam, aspirin, salicylic acid, diflunisal, methyl salicylate, phenylbutazone, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, and the like.

8. Antihistamines, such as diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine, tripelennamine, brompheniramine, hydroxyzine, cyclizine, meclizine, clorprenaline, terfenadine, and chlorpheniramine.

9. Respiratory agents, such as theophilline and β_2-adrenergic agonists such as albuterol, terbutaline, metaproterenol, ritodrine, carbuterol, fenoterol, quinterenol, rimiterol, solmefamol, soterenol, and tetroquinol.

10. Sympathomimetics, such as dopamine, norepinephrine, phenylpropanolamine, phenylephrine, pseudoephedrine, amphetamine, propylhexedrine and epinephrine.

11. Miotics, such as pilocarpine, and the like.

12. Cholinergic agonists, such as choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, and arecoline.

13. Antimuscarinic or muscarinic cholinergic blocking agents such as atropine, scopolamine, homatropine, methscopolamine, homatropine methylbromide, methantheline, cyclopentolate, tropicamide, propantheline, anisotropine, dicyclomine, and eucatropine.

14. Mydriatics, such as atropine, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine and hydroxyamphetamine.

15. Psychic energizers such as 3-(2-aminopropyl)indole, 3-(2-aminobutyl)indole, and the like.

16. Anti-infectives, such as antibiotics, including penicillin, tetracycline, chloramphenicol, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; antibacterials, such as erythromycin and clarithromycin; and other anti-infectives including nitrofurazone and the like.

17. Dermatological agents, such as vitamins A and E.

18. Humoral agents, such as the prostaglandins, natural and synthetic, for example PGE_1, $PGE_2\alpha$, and $PGF_2\alpha$, and the PGE_1 analog misoprostol.

19. Antispasmodics, such as atropine, methantheline, papaverine, cinnamedrine, and methscopolamine.

20. Antidepressant drugs, such as isocarboxazid, phenelzine, tranylcypromine, imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, maprotiline, and trazodone.

21. Anti-diabetics, such as insulin, and anti-cancer drugs such as tamoxifen and methotrexate.

22. Anorectic drugs, such as dextroamphetamine, methamphetamine, phenylpropanolamine, fenfluramine, diethylpropion, mazindol, and phentermine.

23. Anti-allergenics, such as antazoline, methapyrilene, chlorpheniramine, pyrilamine and pheniramine.

24. Tranquilizers, such as reserpine, chlorpromazine, and antianxiety benzodiazepines such as alprazolam, chlordiazepoxide, clorazeptate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam and diazepam.

25. Antipsychotics, such as thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperacetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine, and molindone.

26. Decongestants, such as phenylephrine, ephedrine, naphazoline, tetrahydrozoline.

27. Antipyretics, such as aspirin, salicylamide, and the like.

28. Antimigrane agents, such as dihydroergotamine and pizotyline.

29. Drugs for treating nausea and vomiting, such as chlorpromazine, perphenazine, prochlorperazine, promethazine, triethylperazine, triflupromazine, and trimeprazine.

30. Anti-malarials, such as the 4-aminoquinolines, α-aminoquinolines, chloroquine, and pyrimethamine.

31. Anti-ulcerative agents, such as misoprostol, omeprazole, and enprostil.

32. Peptides, such as growth releasing factor.

33. Drugs for Parkinson's disease, spasticity, and acute muscle spasms, such as levodopa, carbidopa, amantadine, apomorphine, bromocriptine, selegiline (deprenyl), trihexyphenidyl hydrochloride, benztropine mesylate, procyclidine hydrochloride, baclofen, diazepam, and dantrolene.

34. Anti-estrogen or hormone agents, such as tamoxifen or human chorionic gonadotropin.

[0057] The active agents can be present in the composition in different forms, depending on which form yields the optimum delivery characteristics. Thus, in the case of drugs, the drug can be in its free base or acid form, or in the form of salts, esters, or any other pharmacologically acceptable derivatives, or as components of molecular complexes.

[0058] The amount of drug to be incorporated in the composition varies depending on the particular drug, the desired therapeutic effect, and the time span for which the device is to provide therapy. For most drugs, the passage of the drugs through the skin will be the rate-limiting step in delivery. Thus, the amount of drug and the rate of release is typically selected so as to provide transdermal delivery characterized by a zero order time dependency for a prolonged period of time. The minimum amount of drug in the system is selected based on the amount of drug which passes through the skin in the time span for which the device is to provide therapy. Normally, the amount of drug in the system can vary from about 0.3% to about 50% by weight, and preferably, for the lower drug doses permitted by this invention, from about 1.0% to about 30%.

[0059] Of course, the composition of the transdermal drug delivery system can also contain agents known to accelerate the delivery of the drug through the skin. These agents have been referred to as skin-penetration enhancers, accelerants, adjuvants, and sorption promoters, and are collectively referred herein as "enhancers." This class of agents includes those with diverse mechanisms of action including those which have the function of improving the solubility and diffusibility of the drug within the multiple polymer and those which improve percutaneous absorption, for example, by changing the ability of the stratum corneum to retain moisture, softening the skin, improving the skin's permeability, acting as penetration assistants or hair-follicle openers or changing the state of the skin including the boundary layer. Some of these agents have more than one mechanism of action, but in essence they serve to enhance the delivery of the drug.

[0060] Some examples of enhancers are polyhydric alcohols such as dipropylene glycol, propylene glycol, and polyethylene glycol which enhance drug solubility; oils such as olive oil, squalene, and lanolin; fatty ethers such as cetyl ether and oleyl ether; fatty acid esters such as isopropyl myristate which enhance drug diffusibility; urea and urea derivatives such as allantoin which affect the ability of keratin to retain moisture; polar solvents such as dimethyldecylphosphoxide, methyloctylsulfoxide, dimethyllaurylamide, dodecylpyrrolidone, isosorbitol, dimethylacetonide, dimethylsulfoxide, decylmethylsulfoxide, and dimethylformamide which affect keratin permeability; salicylic acid which softens the keratin; amino acids which are penetration assistants; benzyl nicotinate which is a hair follicle opener; and higher molecular weight aliphatic surfactants such as lauryl sulfate salts which change the surface state of the skin and drugs administered. Other agents include oleic and linoleic acids, ascorbic acid, panthenol, butylated hydroxytoluene, tocopherol, tocopheryl acetate, tocopheryl linoleate, propyl oleate, and isopropyl palmitate.

[0061] In certain embodiments of the invention a plasticizer or tackifying agent is incorporated into the formulation to improve the adhesive characteristics of the dermal composition. A tackifying agent is particularly useful in those embodiments in which the drug does not plasticize the polymer. Suitable tackifying agents are those known in the art including: (1) aliphatic hydrocarbons; (2) mixed aliphatic and aromatic hydrocarbons; (3) aromatic hydrocarbons; (4) substituted aromatic hydrocarbons; (5) hydrogenated esters; (6) polyterpenes; and (7) hydrogenated wood rosins. The tackifying agent employed is preferably compatible with the blend of polymers. In preferred embodiments, the tackifying agent is silicone fluid (*e.g.*, 360 Medical Fluid, available from Dow Corning Corporation, Midland, MI) or mineral oil. Silicone fluid is useful for blends comprising polysiloxane as a major component. In other embodiments, where polyacrylate, for example, is a major component, mineral oil is a preferred tackifying agent.

[0062] Some drugs, such as the vasodilator nitroglycerin, function as plasticizers in the composition because they are soluble to a certain degree in the polymers comprising the system. For drug molecules which are not readily soluble in the polymer system, a co-solvent for the drug and polymer can be added. Co-solvents, such as lecithin, retinol derivatives, tocopherol, dipropylene glycol, triacetin, propylene glycol, saturated and unsaturated fatty acids, mineral oil, silicone fluid, alcohols, butyl benzyl phthalate, and the like are useful in the practice of the instant invention depending on the solubility of the drug in the multiple polymer adhesive system.

[0063] To summarize, the preferred and optimum compositions for the polyacrylate/polysiloxane embodiment are as follows:

TABLE II

PERCENT BY WEIGHT		
Component	Preferred Range	Optimum Range
Polysiloxane	97-4	97-14
Polyacrylate	2-95	2-85
Co-solvent(s)	0-30	0-20
Enhancer(s)	0-20	0-10
Drug(s)	0.3-50	1-30

[0064] The composition of this invention may further be provided with various thickeners, fillers and other additives known for use with dermal compositions. Where the composition tends to absorb water, for example, when lecithin is used as a co-solvent, hydrophilic fillers are especially useful. One type of hydrophilic filler which has been successfully employed is an aluminum silicate clay.

[0065] In a device aspect of the invention, the dermal composition can be used as an adhesive portion of any transdermal drug delivery device (*e.g.*, a reservoir device) or it can comprise an adhesive monolithic device. Of course, the principles of the invention would still apply to embodiments where the dermal composition is not a pressure-sensitive adhesive and comprises the drug reservoir.

[0066] Reference to FIG. 1 shows a schematic illustration of an adhesive monolithic device embodiment of the invention 10. The dermal composition comprises a monolithic body 11 of a defined geometric shape with a protective release liner 12 on one side of monolithic body 11 and a backing layer 13 on the other side. Removal of the release liner 12 exposes the pressure-sensitive multiple polymer adhesive which functions both as the drug carrier matrix and as the means of applying the system to the patient.

[0067] A device, or individual dosage unit, of the present invention can be produced in any manner known to those of skill in the art. After the dermal composition is formed, it may be brought into contact with the backing layer in any manner known to those of skill in the art. Such techniques include calender coating, hot melt coating, solution coating, *etc.* Of course, backing materials are well known in the art and can comprise plastic films of polyethylene, vinyl acetate resins, ethylene/vinyl acetate copolymers, polyvinyl chloride, polyurethane, and the like, metal foils, non-woven fabric, cloth and commercially available laminates. The backing material generally has a thickness in the range of 2 to 1000 micrometers and the dermal composition is generally disposed on backing material in a thickness ranging from about 12 to 250 micrometers thick.

[0068] Suitable release liners are also well known in the art and include the commercially available products of Dow Corning Corporation designated Bio-Release® liner and Syl-off® 7610 liner. For preferred embodiments in which a polysiloxane is part of the multiple polymeric adhesive system, the release liner must be compatible with the silicone adhesive. An example of a suitable commercially available liner is 3M's 1022 Scotch Pak.

[0069] The configuration of the transdermal delivery system of the present invention can be in any shape or size as is necessary or desirable. Illustratively, a single dosage unit may have a surface area in the range of 1 to 200 cm^2. Preferred sizes are from 5 to 60 cm^2.

[0070] In a method aspect of the invention, a plurality of polymers having differing solubility parameters are blended (but not chemically reacted or cross-linked) to result in a dermal composition, or multiple polymer adhesive system with incorporated drug or bioactive agent, which controls delivery of an incorporated drug into and through the epidermis. The blending of polymers results in an adjustment of the saturation concentration of the drug in the polymeric system and therefore permits selective modulation of the transdermal drug delivery rate. The term "blending," of course, incorporates choosing the appropriate polymeric components, and the proportions thereof, to achieve the desired effect.

[0071] In a preferred embodiment of the invention, a dermal composition is prepared by mixing the polyacrylate, the polysiloxane, drug, co-solvent(s), and tackifying agent, if needed, in an appropriate volatile solvent(s), then casting the mixture and removing the solvent(s) by evaporation to form a film.

[0072] Suitable volatile solvents include, but are not limited to, alcohols such as isopropanol and ethanol; aromatics such as xylenes and toluene; aliphatics such as hexane, cyclohexane, and heptane; and alkanoic acid esters such as ethyl acetate and butyl acetate.

[0073] An exemplary general method of preparation is as follows:

1. Appropriate amounts of polysiloxane and polyacrylate, dissolved in a solvent(s), are combined and thoroughly mixed together in a vessel.
2. The drug is then added to the polymer mixture and agitation is carried out until the drug is uniformly mixed in.
3. Co-solvents and enhancers, if necessary, can then be added to the drug-polymer mixture, and thoroughly mixed.

4. The formulation is then transferred to a coating operation where it is coated onto a protective release liner at a controlled specified thickness.
5. The coated product is then passed through an oven in order to drive off all volatile processing solvents.
6. The dried product on the release liner is then joined to the backing material and wound into rolls for storage.
7. Appropriate size and shape dosage units are die-cut from the roll material and then pouched.

[0074] The order of steps, the amounts of ingredients, and the amount and time of agitation or mixing are process variables which will depend on the specific polymers, drug, co-solvents, and enhancers used in the formulation. These factors can be adjusted by those of skill in the art as required to provide a uniform product which has acceptable pressure-sensitive adhesive characteristics.

Examples

[0075] The following specific examples are included as illustrative of dermal compositions, and methods of making same, within the contemplation of the invention. These examples are in no way intended to be limiting of the scope of the invention.

[0076] The following commercially available adhesives were used in the blends comprising the multiple polymer adhesive system of the examples: "Duro-Tak 80-1194, 80-1196, and 80-1197" are trademarks of National Starch and Chemical Corporation, Bridgewater, New Jersey for acrylic adhesives (polyacrylates) in organic solutions.

[0077] "BIO-PSA X7-3027, X7-4919, X7-2685, and X7-3122" are trademarks of Dow Corning Corporation, Medical Products, Midland, Michigan for silicone adhesives (polysiloxanes) in organic solutions. BIO-PSA-3027 is particularly suitable for use in formulations containing amine-functional drugs, such as albuterol and pilocarpine, in the following examples.

[0078] "Vistanex LM-LS-LC" is a trademark of Exxon Chemical Company, Houston, Texas, for a polyisobutylene polymer with a Flory molecular weight of 42,600 to 46,100.

[0079] "Elvax 40-W" is a trademark of Du Pont Company, Wilmington, Delaware, for a polyethylene/vinyl acetate copolymer (40% vinyl acetate content).

[0080] The aforementioned polymeric adhesives are supplied, or prepared, as solutions wherein the percent solids by weight are as follows:

Ingredient	Percent Solids
BIO-PSA X7-3027	50
BIO-PSA X7-3122	65
BIO-PSA X7-4919	50
BIO-PSA X7-2685	50
Duro-Tak 80-1194	45
Duro-Tak 80-1196	45
Duro-Tak 80-1197	45
Elvax 40-W	30
Vistanex LM-MS-LC	30

[0081] "360 Medical Fluid" is a trademark of Dow Corning Corporation for a polydimethylsiloxane fluid. In certain embodiments of the invention, 360 Medical Fluid is added as a tackifier to improve the adhesive characteristics of the end product.

EXAMPLE 1

[0082] A nitroglycerin-polymer mixture was prepared by combining 22.0 parts of nitroglycerin, 1.0 part of dipropylene glycol, 1.3 parts of lecithin, 0.8 parts of propylene glycol, 2.5 parts of 360 Medial Fluid (1000 cs), 1.0 part of bentonite, 63.6 parts of polyacrylate (Duro-Tak 80-1194), and 85.6 parts of polysiloxane (BIO-PSA X7-4919), and mixed well in an appropriate container. Nitroglycerin is available as a solution in solvents such as ethanol, toluene, and propylene glycol from ICI Americas Inc., Wilmington, Delaware. In this instance, the nitroglycerin was added as a solution in toluene mixed together with the polyacrylate. The resulting composition had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, shown below.

COMPONENT	PERCENT BY WEIGHT
Polysiloxane (Dow Corning Silicone Adhesive X7-4919)	42.8
Polyacrylate (National Starch Acrylic Adhesive, Duro-Tak 80-1194)	28.6
Polydimethylsiloxane fluid (Dow Corning 360 Medical Fluid)	2.5
Lecithin	1.3
Propylene glycol	0.8
Dipropylene glycol	1.0
Bentonite	1.0
Nitroglycerin	22.0
	100.0

[0083] Nitroglycerin flux results through cadaver skin *in vitro* from the formulation of Example 1, Transderm-Nitro® (a trademark of Ciba-Geigy Corporation, Summit, NJ), and Nitro-Dur® (a trademark of Key Pharmaceuticals, Inc., Kenilworth, NJ) are summarized in FIG. 2. As shown in FIG. 2, nitroglycerin flux from the dermal composition of Example 1 (20.8 $\mu g/cm^2hr$) was approximately twice that from Transderm-Nitro® (9.5 $\mu g/cm^2hr$) and about 1.5 times that from Nitro-Dur® (13.4 $\mu g/cm^2hr$).

EXAMPLES 2 - 5

[0084] In the following examples (2-5), the method of Example 1 was used with the appropriate amounts of starting materials to yield compositions having the following ingredient concentrations set forth in tabular form in TABLE III. Example 2 is presented for comparative purposes and its formulation is not within the scope of the present invention. Example 3 and 5 are adhesive compositions comprising blends of polyacrylate and a second polymer selected to illustrate the principles of the invention. All other components, such as excipients or fillers, remain constant in composition and amount from Examples 2 to 5.

TABLE III

	Examples (%, w/w)			
Ingredient (SP, $J^{1/2}/cm^{3/2}$)	2	3	4	5
Polyacrylate (21)	73.2	33.1	33.1	33.1
Polyethylene vinyl acetate (21)	--	40.1	-	--
Polyisobutylene (17)	--	--	40.1	--
Polysiloxane (15)	--	--	-	40.1
Nitroglycerin (27)	20.8	20.8	20.8	20.8
Oleic acid	2.0	2.0	2.0	2.0
Propylene glycol	0.8	0.8	0.8	0.8
Lecithin	1.2	1.2	1.2	1.2
Dipropylene glycol	1.0	1.0	1.0	1.0
Bentonite	1.0	1.0	1.0	1.0

[0085] FIG. 3 graphically summarizes the *in vitro* nitroglycerin flux results through cadaver epidermis from the dermal compositions of Examples 2 to 5. As seen in FIG. 3, addition of either polyisobutylene (Example 4) or polysiloxane (Example 5) -- both with SPs lower than polyacrylate -- resulted in doubling of the nitroglycerin flux as compared to an all acrylate system (Example 2). However, addition of polyethylene vinyl acetate (Example 3) -- with an SP value similar to the polyacrylate -- resulted in little effect on nitroglycerin flux as compared to the system of Example 2. Thus, the formulation of Example 3 is not within the scope of the present invention.

EXAMPLE 6

[0086] A series of nitroglycerin-containing compositions (I-VI) were prepared in which the polyacrylate (X7-3122) to polysiloxane (Duro-Tak 80-1194) ratio was varied from 100.0 : 0.0 (all acrylic) to 0.0 : 100.0 (all siloxane) by weight. Nitroglycerin concentration was held at 20% for all compositions. The ingredient concentrations of these compositions are shown below in TABLE IV.

TABLE IV

	I	II	III	IV	V	VI
Polysiloxane	-	14.4	28.8	43.2	57.6	72.6
Silicone Fluid	--	1.6	3.2	4.8	6.4	8.0
Polyacrylate	80.0	64.0	48.0	32.8	16.0	--
Nitroglycerin	20.0	20.0	20.0	20.0	20.0	20.0

[0087] *In vitro* skin flux was determined for these compositions and the results are summarized in Table V and graphically depicted in FIG. 4.

TABLE V

	% of Polymer		(µg/cm 2/hr) (hr)	
Composition	Polyacrylate	Polysiloxane	GTN Flux	Tlag
I	100	0	1.6	0.0
II	81.6	18.4	3.2	1.5
III	62.5	37.5	4.2	2.0
IV	43.2	56.8	4.5	2.3
V	21.7	78.3	5.2	2.3
VI	0	100	4.9	2.4
Nitro-Dur®	-	-	3.0	2.5

[0088] As shown, nitroglycerin (GTN) flux increased as the concentration of polysiloxane in the multiple polymer adhesive matrix increased up to a maximum, at around 80% polysiloxane, after which no more increase in flux was seen. It appears that beyond a certain concentration of siloxane polymer, the nitroglycerin activity ceases to increase (unit activity is reached), and the flux no longer increases. The attainment of saturation concentration (unit activity) is further verified by the fact that Composition VI had nitroglycerin exudate; that is, the surface of the adhesive was "wet" with excess nitroglycerin. Of course, Composition VI, which is all polysiloxane, is not within the contemplation of the invention.

[0089] The composition of the blend of polymers is preferably chosen so that the flux rate of drug from the blend is at a maximum. Studies similar to those reported herein may be employed to assist in selecting the appropriate components of the blend and the weight ratios thereof. In alternative embodiments, it may be desirable to select a composition in which the flux rate will be retarded.

EXAMPLES 7 - 9

[0090] An estradiol-polymer mixture (Example 7) was prepared by combining 2.0 parts of 17β-estradiol, 2.0 parts of propylene glycol, 3.0 parts of lecithin, 5.0 parts of oleic acid, 5.0 parts of dipropylene glycol, 93.3 parts of polyacrylate (Duro-Tak 80-1196), and 63.1 parts of polysiloxane (BIO-PSA X7-3122), and mixing well in an appropriate container. The resulting composition had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in TABLE VI.

[0091] Examples 8 and 9 were made in accordance with the method of Example 7. The compositions of Examples 8 and 9 have the same drug and additional components, such as the co-solvents, as Example 7, but are not within the scope of this invention inasmuch as the resulting adhesive matrices are single polymer systems. Examples 8 and 9 are given for comparative purposes only.

TABLE VI

	Examples (%, w/w)		
Ingredient	7	8	9
Polyacrylate	42.0	83.0	-
Polysiloxane	41.0	--	83.0
Estradiol	2.0	2.0	2.0
Oleic acid	5.0	5.0	5.0
Propylene glycol	2.0	2.0	2.0
Lecithin	3.0	3.0	3.0
Dipropylene glycol	5.0	5.0	5.0

[0092] Estradiol flux *in vitro* from the systems of Examples 7, 8, and 9 is shown in FIG. 5. As seen in FIG. 5, delivery from the system of this invention utilizing the multiple polymer adhesive (polyacrylate/polysiloxane) of Example 7 was substantially greater than delivery from the prior art systems comprising single polymer adhesives (Examples 8 and 9).

EXAMPLES 10 - 13

[0093] In the following examples (10-13), the method of Example 7 was used with the appropriate amounts of starting materials to yield compositions having the ingredient concentrations set forth in TABLE VII.

TABLE VII

	Examples (%, w/w)			
Ingredient	10	11	12	13
Polysiloxane	18.0	33.5	39.5	58.0
Polyacrylate	65.0	39.5	33.5	15.0
Estradiol	2.0	2.0	2.0	2.0
Oleic acid	5.0	5.0	5.0	5.0
Propylene glycol	2.0	2.0	2.0	2.0
Lecithin	3.0	3.0	3.0	3.0
Silicone fluid	5.0	15.0	15.0	15.0

[0094] FIG. 6 shows estradiol flux results for the compositions of Examples 10 - 13; average flux was calculated for each composition from 0 to 22 hours and from 22 to 99 hours from the start of the study. As seen in FIG. 6, estradiol flux progressively increased with increased silicone polymer content during the first 22 hours of delivery, but was affected to a much lesser degree during the remainder of the study (22 to 99 hours). Thus, significant adjustment of the estradiol delivery rate during the initial phase of delivery was accomplished, with minor effects on the later delivery phase, by modulating the polysiloxane to polyacrylate polymer ratio. Fig 6 also illustrates that the delivery characteristics over time can be adjusted by the appropriate choice of polymers and respective weight ratios. For example, the formulation of Example 10 delivers drug at approximately the same rate over time whereas the formulation of Example 13 delivers more quickly in the early phase than the latter.

EXAMPLES 14 - 16

[0095] A norethindrone acetate-polymer mixture was prepared by combining 0.6 parts of norethindrone acetate, 1.0 parts of butylene glycol, and 40.9 parts of polyacrylate (Duro-Tak 80-1194), and mixing well in an appropriate container. The resulting composition had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in TABLE VIII. The same method was employed to make Examples 15 and 16.

TABLE VIII

	Examples (% w/w)		
Ingredient	14	15	16
Polyacrylate	92.0	--	46.0
Polysiloxan	--	92.0	46.0
Norethindrone acetate	3.0	3.0	3.0
Butylene glycol	5.0	5.0	5.0

[0096] Norethindrone acetate flux *in vitro* from the systems of Examples 14, 15, and 16 is shown in FIG. 7. As seen in FIG. 7, norethindrone acetate delivery from the polyacrylate/polysiloxane systems of this invention (Example 16) was intermediate to delivery from the single polymer systems not of this invention (Example 14 and 15). Thus, blending the polyacrylate and polysiloxane results in modulation of the norethindrone acetate flux.

EXAMPLES 17 - 20

[0097] As estradiol/norethindrone acetate combination-polymer mixture was prepared by combining 0.6 parts of 17β estradiol, 0.6 parts of norethindrone acetate, 0.6 parts of butylene glycol, 0.6 parts of oleic acid, 1.5 parts of lecithin, 4.5 parts of silicone fluid (polydimethylsiloxane fluid, Dow Corning 360 Medical Fluid, 100 cs), and 43.2 parts of polysiloxane (BIO-PSA X7-4919), and mixing well in an appropriate container. The method of Example 17 was used with the appropriate amounts of starting materials to yield the compositions of Example 18, 19 and 20. The polyacrylate used in Examples 18-20 was National Starch Acrylic Adhesive, Duro-Tak 80-1197. The resulting compositions had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in TABLE IX.

TABLE IX

	Examples (% w/w)			
Ingredient	17	18	19	20
Polysiloxan	72.0	68.0	60.0	47.0
Polyacrylate	--	5.0	15.0	30.0
Estradiol	2.0	2.0	2.0	2.0
Norethindrone acetate	2.0	2.0	2.0	2.0
Oleic acid	2.0	2.0	2.0	2.0
Butylene glycol	2.0	2.0	2.0	2.0
Lecithin	5.0	5.0	5.0	5.0
Silicone fluid	15.0	14.0	12.0	10.0

[0098] Flux results for the compositions of Examples 17-20 are shown in Fig. 8. As shown in Fig. 8, the flux of both estradiol (E2) and norethindrone acetate (NAc) varied as the polysiloxane to polyacrylate polymer ratio was adjusted; estradiol flux gradually increased and then decreased with a maximum at about 15% acrylate, and the norethindrone acetate flux continuously decreased with increasing acrylate content as would be expected from the data of Fig. 7. A further effect of varying the polysiloxane/polyacrylate polymer ratio is exhibited by a plot of estradiol flux relative to norethindrone acetate flux (estradiol flux divided by norethindrone acetate flux) as shown in Fig. 9. By adjusting the silicone to acrylate polymer ratio, it was possible to modulate the relative delivery of two drugs (estradiol and norethindrone acetate) from the systems of this invention.

EXAMPLES 21 - 23

[0099] A pilocarpine-polymer mixture was prepared by combining 5.0 parts of pilocarpine base, 1.2 parts of lecithin, 0.8 parts of propylene glycol, 2.0 parts of oleic acid, 2.5 parts of silicone fluid (polydimethylsiloxane, Dow Corning 360 Medical Fluid, 100 cs), and 77.0 parts of polysiloxane (Dow Corning Silicone Adhesive BIO-PSA X7-3027), and mixing well in an appropriate container. Example 22 incorporated pilocarpine into a polyacrylate comprising National Starch Acrylic Adhesive, Duro-Tak 80-1196. Example 23 employed a blend of polysiloxane and polyacrylate in accordance with the principles of the invention. The resulting compositions had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in TABLE X.

TABLE X

	Examples (% w/w)		
Ingredient	21	22	23
Polyacrylate	--	82.0	41.0
Polysiloxane	77.0	--	41.0
Silicone Fluid	5.0	--	--
Pilocarpine	10.0	10.0	10.0
Oleic acid	4.0	4.0	4.0
Propylene glycol	1.6	1.6	1.6
Lecithin	2.4	2.4	2.4

[0100] Pilocarpine flux *in vitro* from the systems of Examples 21, 22, and 23 is shown in Fig. 10. As seen in Fig. 10, the delivery rate from the system of this invention utilizing the multiple polymer adhesive (polyacrylate/polysiloxane) of Example 23, was intermediate of the delivery rates from single polymer compositions (Examples 21 and 22) which are not of this invention. In this embodiment of the invention, the combination of polyacrylate and polysiloxane polymers adjusted the delivery of rate of pilocarpine within the ranges established by single polymer compositions.

EXAMPLES 24 - 27

[0101] An albuterol-polymer mixture was prepared by combining 10.2 parts of albuterol base, 1.5 parts of lecithin, 1.0 part of propylene glycol, 4.1 parts of oleic acid, 2.6 parts of dipropylene glycol, 1.5 parts of butylene glycol, 1.5 parts of vitamin E acetate (tocoperyl acetate), 25.5 parts of polyacrylate (Duro-Tak 80-1196), 11.9 parts of polysiloxane A (BIO-PSA X7-3122), 20.1 parts of polysiloxane B (BIO-PSA X7-3027), and 20.1 parts of isopropyl alcohol, and mixing well in an appropriate container. The resulting composition had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in Table XI.

[0102] The method of Example 24 was used with the appropriate amounts of starting materials to yield the compositions of Examples 25, 26, and 27.

TABLE XI

	Examples (% w/w)			
Ingredient	24	25	26	27
Polysiloxane A	14.0	13.8	14.0	14.0
Polysiloxane B	19.6	19.2	28.0	19.6
Polyacrylate	22.4	22.0	20.0	22.4
Albuterol	20.0	20.0	20.0	20.0
Oleic acid	8.0	8.0	8.0	8.0
Propylene glycol	2.0	2.0	2.0	2.0
Dipropylene glycol	5.0	5.0	5.0	5.0
Butylene glycol	3.0	3.0	--	3.0
Vitamin E acetate	3.0	3.0	--	--
Vitamin E	--	1.0	--	--
Vitamin E linoleate	--	--	--	3.0
Lecithin	3.0	3.0	3.0	3.0

[0103] Albuterol flux results through human cadaver skin *in vitro* from the formulations of Examples 24, 25, 26, and 27, are summarized in Fig. 11; nitroglycerin flux from Nitro-Dur® through the same skin specimen is shown as a control. Flux values for the albuterol compositions of Example 24 to 27 ranged from about 17 $\mu g/cm^2/hr$ to about 22 $\mu g/cm^2/hr$. The nitroglycerin flux value of about 28 $\mu g/cm^2/hr$ was slightly higher than the literature delivery rate for this product (20 $\mu g/cm^2/hr$, based on Nitro-Dur® product label of 0.1 mg/hr from a 5 cm^2 system). In order to adjust for the apparent higher permeability of the skin specimen, albuterol flux results can be multiplied by an adjustment factor of 0.714 (20/28); this would result in flux values of about 12 $\mu g/cm^2/hr$ to about 16 $\mu g/cm^2/hr$.

[0104] Therapeutic albuterol plasma concentrations are in the range of about 4 to 8 ng/mL, and are produced by

delivery rates of about 115 to 230 μg/hr. The flux rates (12 to 16 μg/cm^2/hr) obtained from the compositions of this invention therefore would produce the necessary albuterol plasma levels (4 to 8 ng/mL) for the treatment of asthma from system sizes of about 10 to 20 cm^2.

EXAMPLES 28 - 29

[0105] Estradiol-polymer mixtures were prepared in accordance with the method of Example 7. Example 28 is illustrative of a multiple polymer adhesive system where polyacrylate is blended with polyisobutylene (Vistanex LM-LS-LC). The resulting compositions had the ingredient concentrations on a "dry" basis, that is, after removal of volatile process solvents, given below in TABLE XII.

TABLE XII

	Examples (%, w/w)	
Ingredient	28	29
Polyacrylate	45.0	45.0
Polyisobutylene	45.0	–
Polysiloxane	--	45.0
Estradiol	2.0	2.0
Oleic acid	5.0	5.0
Lecithin	3.0	3.0

[0106] Estradiol flux *in vitro* from the systems of Examples 28 and 29 are shown in FIG. 12. As seen in FIG. 12, delivery from the multiple polymer adhesive system of Example 28 is comparable to delivery from Example 29.

EXAMPLE 30

[0107] In addition to flux measurements, the apparent diffusion coefficient, D, was calculated from release data for nitroglycerin from matrices of Compositions I to VI (Example 6) into an infinite sink. The method of D.R. Paul, Controlled Release Polymeric Formulations, ACS Symposium Series No. 33, Chapter 1 (1976) was used wherein the initial concentration of nitroglycerin in the matrix, C_0, was determined (assuming a density of 1.0) and the relationship of the amount released, M_t, by a matrix of area, A, and the diffusion coefficient is defined by:

$$M_t/A = 2C_o (Dt/\pi)^{1/2}$$

[0108] Plotting, M_t/A against $t^{1/2}$, results in a graph having a slope, m, defined by:

$$m = 2C_o (D/\pi)^{1/2}$$

[0109] The value of m can be ascertained by linear regression to get the slope of the best fit line. The diffusion coefficient is calculated as:

$$D = \pi(m/2C_o)^2$$

[0110] The results of these calculations for Compositions I to VI are shown below in Table XII.

TABLE XIII

Composition	C_o(mg/cm^3)m	(mg/cm^{2}h$^{1/2}$)	D(cm^2/sec)	D(x10^9)
I	241.0	0.8728	2.861 x 10^{-9}	2.86
II	233.3	0.9483	3.605 x 10^{-8}	36.05
III	231.3	1.0834	4.786 x 10^{-8}	47.86
IV	219.7	1.2502	7.065 x 10^{-8}	70.65

TABLE XIII (continued)

Composition	C_o(mg/cm^3)m	(mg/cm^{2}h$^{1/2}$)	D(cm^2/sec)	D(x10^9)
V	217.0	1.5920	1.174×10^{-7}	117.4
VI	215.0	2.4551	2.845×10^{-7}	284.5
Nitro-Dur	380.0	1.4680	3.256×10^{-8}	32.56

[0111] FIGS. 13 and 14 show the relationship of flux rate (J) plotted against apparent diffusion coefficient (D) and net solubility parameter (SP), respectively, for Compositions I-VI. The net solubility parameter, SP_{nct}, was calculated using a weighted average of the solubility parameters of the individual polymers comprising the matrix:

$$SP_{nct} = \emptyset_{ps} SP_{ps} + \emptyset_{pa} SP_{pa},$$

where $\emptyset_{ps}$ is the weight percentage of polysiloxane and SP_{ps} is the solubility parameter of polysiloxane. The subscript "pa" refers to the polyacrylate. FIG. 15 is a plot of diffusion coefficient versus net solubility parameter.

Claims

1. A pressure-sensitive transdermal drug delivery system comprising a pressure-sensitive adhesive dermal composition in which a drug is incorporated, **characterized in that** the pressure-sensitive adhesive dermal composition comprises a blend of:

   (a) a polyacrylate having a first solubility and a second polymer having a second solubility selected from the group consisting of a polysiloxane and a hydrocarbon polymer; and
   (b) a therapeutically effective amount of a drug for transdermal administration,

   wherein the polyacrylate and the second polymer modulates the permeation rate of the drug through the dermis by adjusting the solubility of the drug in the system, and wherein the composition excludes ethylene vinyl acetate polymers.

2. The system of claim 1, **characterized in that** the polymers of the blend consist of the polyacrylate and second polymer.

3. The system as claimed in claims 1 and 2, **characterized in that** the polymers of the blend consist of the polyacrylate and the hydrocarbon polymer.

4. The system as claimed in any of claims 1 to 3 inclusive, **characterized in that** the hydrocarbon polymer is selected from the group consisting of polyethylene, polystyrene, polyisobutylene, polybutadiene and the copolymer of polyethylene/butylene.

5. The system as claimed in any of claims 1 to 4 inclusive, **characterized in that** the hydrocarbon polymer is polyisobutylene.

6. The system of claims 1 and 2, **characterized in that** the polymers of the blend consist of the polysiloxane and the polyacrylate.

7. The system of claim 6, **characterized in that** the polyacrylate is present in an amount ranging from about 2% to about 96% by weight of the system and the polysiloxane is present in an amount ranging from about 98% to about 4% by weight of the system.

8. The system of claim 6, **characterized in that** the system comprises based on the total weight of the system, about 0.3 to about 50% by weight of albuterol, about 14 to about 97% by weight of polysiloxane, about 2 to about 85% by weight of polyacrylate, 0 to about 20% by weight of enhancers, and about 0 to about 30% by weight of cosolvents.

9. The system of claim 6, **characterized in that** the system comprises based on the total weight of the system, about

0.3 to about 50% by weight of said drug, about 14 to about 97% by weight of polysiloxane, about 2 to about 85% by weight of polyacrylate, 0 to about 20% by weight of enhancers, and about. 0 to about 30% by weight of cosolvents.

10. The system of claim 1, **characterized in that** the blend includes additional polymers.

11. The system of any of claims 1 to 10 inclusive, **characterized in that** the composition further comprises a hydrophilic filler.

12. The system of claim 11, **characterized in that** the hydrophilic filler includes aluminum silicate clay.

13. The system of any of claims 1 to 12 inclusive, **characterized in that** the system further comprises a backing material superimposed on one surface of the pressure-sensitive adhesive system, said backing material being substantially impermeable to the drug contained therein.

14. The system of claim 13, **characterized in that** the system further comprises a release liner superimposed on a surface of the pressure sensitive adhesive system opposite said backing material.

15. The system of any of claims 1 to 14 inclusive, **characterized in that** the drug is a steroid.

16. The system of claim 15, **characterized in that** the steroid is an estrogen selected from the group consisting of conjugated estrogens, esterified estrogens, estropipate, 17β-estradiol, equilin, mestranol, estrone, estriol, ethinyl estradiol, and diethylstilbestrol.

17. The system of claim 15, **characterized in that** the steroid is a progestational agent.

18. The system of claim 17, **characterized in that** the progestational agent is selected from the group consisting of progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chloromadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α-hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, demegestone, promegestone, and megestrol acetate.

19. The system of any of claims 1 to 14 inclusive, **characterized in that** the drug is a β_2-adrenergic agonist.

20. The system of claim 19, **characterized in that** the β_2-adrenergic agonist is selected from the group consisting of metaproterenol, terbutaline, albuterol, carbuterol, rimiterol, salmefamol, fenoterol, soterenol, tratoquinol, and quinterenol.

21. The system of any of claims 1 to 14 inclusive, **characterized in that** the drug is a cardioactive drug.

22. The system of claim 21, **characterized in that** said cardioactive agent is selected from the group consisting of nitroglycerin, isosorbide dinitrate, isosorbide mononitrates, quinidine sulfate, procainamide, benzydroflumethiazide, bendroflumethiazide, chlorothiazide, nifedipine, nicardipine, verapamil, diltiazem, timolol, propranolol, captopril, clonidine and prazosin.

23. The system of any of claims 1 to 14 inclusive, **characterized in that** the drug is a cholinergic agonist.

24. The system of claim 23, **characterized in that** the cholinergic agonist is selected from the group consisting of choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, and arecoline.

25. The system of any of claims 1 to 24 inclusive, **characterized in that** the drug is intimately mixed with the blend.

26. The system of any of claims 1 to 25 inclusive, **characterized in that** the polyacrylate comprises at least 50 % by weight of an acrylate or alkyl acrylate monomer.

27. The system of claim 16, **characterized in that** the estrogen is 17β-estradiol and the 17β-estradiol is present in the system in an amount of from about 1% to about 5% by weight.

28. The system of claim 18, **characterized in that** the progestational agent is norethindrone acetate and the norethindrone acetate is present in the system in an amount of from about 1% to about 5% by weight.

29. The system of claim 20, **characterized in that** the β_2-adrenergic agonist is albuterol and the albuterol is present in the system in an amount of less than about 30% by weight.

30. The system of claim 22, **characterized in that** the cardioactive agent is nitroglycerin and the nitroglycerin is present in the system in an amount of less than about 25% by weight.

31. The system of claim 23, **characterized in that** the cholinergic agonist is pilocarpine and the pilocarpine is present in the system in an amount of less than about 30% by weight.

32. The system of any of claims 1 to 14 inclusive, **characterized in that** the drug is a tranquilizer.

33. The system of claim 32, **characterized in that** the tranquilizer is selected from the group consisting of alprazolam, chlordiazepoxide, clorazeptate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam and diazepam.

34. The system of claim 33, **characterized in that** the tranquilizer is alprazolam.

35. The system of any of claims 1 to 14 inclusive, **characterized in that** the drug is an antipsychotic.

36. The system of claim 35, **characterized in that** the antipsychotic is selected from the group consisting of thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperacetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine and molindone.

37. The system of claim 36, **characterized in that** the antipsychotic is haloperidol.

38. The system of any of claims 1 to 14 inclusive, **characterized in that** the drug is an anesthetic.

39. The system of claim 38, **characterized in that** the anesthetic is selected from the group consisting of lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine and benzocaine.

40. The system of claim 39, **characterized in that** the anesthetic is lidocaine.

41. The system of any of claims 1 to 14 inclusive, **characterized in that** the drug is an analgesic.

42. The system of claim 41, **characterized in that** the analgesic is selected from the group consisting of fentanyl, buprenorphine and codeine.

43. The system of any of claims 1 to 14 inclusive, **characterized in that** the drug has an action on the central nervous system.

44. The system of claim 43, **characterized in that** the drug is nicotine.

45. The system of any of claims 1 to 14 inclusive, **characterized in that** the composition includes a mixture of at least two drugs.

46. The system of claim 45, **characterized in that** the at least two drugs include a progestational agent and an estrogen.

47. The system of claim 46, **characterized in that** said progestational agent is selected from the group consisting of progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chloromadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α-hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, and megestrot acetate.

48. The system of claim 47, **characterized in that** said progestational agent is norethindrone acetate.

49. The system of claim 47, **characterized in that** said estrogen is selected from the group consisting of conjugated estrogens, esterified estrogens, estropipate, 17β-estradiol, equilin, mestranol, estrone, estriol, ethinyl estradiol, and diethylstilbestrol.

50. The system of claim 49, **characterized in that** said estrogen is 17β-estradiol.

51. The system of any of claims 1 to 6 and 10 to 14, **characterized in that** said system achieves an increased permeation rate of the drug through the dermis of a subject relative to the permeation rate achieved by a system comprising one of said polyacrylate or said second polymer as the sole polymer.

52. The system of any of claims 1 to 6 and 10 to 14 inclusive, **characterized in that** said system achieves a decreased permeation rate of the drug through the dermis of a subject relative to the permeation rate achieved by a system comprising said one of said polyacrylate or said second polymer as the sole polymer.

53. The system of any of claims 1 to 7, **characterized in that** the composition further comprises an additive selected from the group consisting of an enhancer, a filler, a co-solvent and an excipient.

54. The system of any of claims 1 to 53 inclusive, **characterized in that** the polyacrylate and the second polymer are pressure-sensitive adhesives.

55. A pressure-sensitive transdermal drug delivery system as claimed in claim 1, **characterized in that** the pressure-sensitive adhesive dermal composition comprises a blend of:

(a) two polymers consisting essentially of about 2% to about 96% by weight of a polyacrylate and about 98% to about 4% by weight of a polysiloxane, the two polymers being in an amount of about 99% to about 50% by weight of said system;
(b) a drug in the amount of about 0.3% to about 50% by weight of said system;
(c) an effective amount of a co-solvent for the drug, said amount being up to about 30% by weight of said system; and
(d) an effective amount of an enhancer, said amount being up to about 20% by weight of said system.

56. The system of claim 55, **characterized in that** composition further comprises fillers and excipients in an amount of about 1% to about 15% by weight of the dermal adhesive system.

57. A pressure-sensitive transdermal drug delivery system as claimed in claim 1, **characterized in that** the pressure-sensitive adhesive dermal composition comprises a blend of:

(a) a polyacrylate having a first solubility parameter and a second polymer selected from the group consisting of polysiloxane and hydrocarbon polymers having a second solubility parameter, wherein the first and second solubility parameters are different from one another by an increment of at least 4 $(J/cm^3)^{1/2}$; and
(b) a therapeutically effective amount of a drug for transdermal administration,

wherein the polyacrylate and the second polymer modulates the permeation rate of the drug through the dermis, and wherein the system excludes an ethylene/vinyl acetate copolymers.

58. A pressure-sensitive transdermal drug delivery system as claimed in claim 1, **characterized in that** the pressure-sensitive adhesive dermal composition comprises a blend of:

(a) a polyacrylate and a second polymer selected from the group consisting of polytetrafluoroethylene, polyvinylchloride, polyvinylidene chloride, polychloroprene, polyacrylonitrile, nylon-6,6, epoxy resin, and a copolymer of polybutadiene/acrylonitrile; and
(b) a therapeutically effective amount of a drug for transdermal administration,

wherein the polyacrylate and the second polymer modulates the permeation rate of the drug through the dermis, and wherein the system excludes an ethylene/vinyl acetate copolymer.

59. A method of modulating the delivery rate of a drug from a transdermal drug delivery system comprising a pressure-sensitive adhesive composition in which a drug is incorporated, **characterized in that** the method comprises the steps of:

a) selecting two or more essentially immiscible or insoluble polymeric materials as components of a multiple polymer adhesive system such that the system has a net solubility parameter which results in a modified solubility of a drug in the composition; and
b) combining said two or more polymeric materials with a drug to form a pressure-sensitive adhesive matrix system, wherein the matrix system achieves a drug delivery rate which is determined by said net solubility parameter and which differs from the delivery rate achieved by a pressure-sensitive adhesive matrix system comprising a single one of said at least two polymeric materials as the sole polymeric material.

60. The method of claim 59, **characterized in that** the drug is intimately mixed with the two or more polymers in the pressure-sensitive adhesive matrix.

61. The method of claim 60, **characterized in that** said step of selecting comprises the step of measuring the flux rate from various weight ratios of the selected two or more polymers and choosing the ratio producing a preselected flux rate.

Patentansprüche

1. Haftklebendes transdermales Wirkstoffabgabesystem, das eine dermale Haftkleberzusammensetzung umfasst, in die ein Wirkstoff eingebaut ist, **dadurch gekennzeichnet, dass** die dermale Haftkleberzusammensetzung ein Gemisch umfasst aus:

(a) einem Polyacrylat, das eine erste Löslichkeit aufweist, und einem zweiten Polymer, das eine zweite Löslichkeit aufweist und das aus der Gruppe ausgewählt ist, die aus einem Polysiloxan und einem Kohlenwasserstoffpolymer besteht; und

(b) einer therapeutisch wirksamen Menge eines Wirkstoffs für die transdermale Verabreichung;

wobei das Polyacrylat und das zweite Polymer die Permeationsrate des Wirkstoffs durch die Dermis modulieren, indem sie die Löslichkeit des Wirkstoffs in dem System regulieren, und wobei die Zusammensetzung keine Ethylen-Vinylacetat-Polymere enthält.

2. System gemäß Anspruch 1, **dadurch gekennzeichnet, dass** die Polymere des Gemischs aus dem Polyacrylat und dem zweiten Polymer bestehen.

3. System gemäß Anspruch 1 und 2, **dadurch gekennzeichnet, dass** die Polymere des Gemischs aus dem Polyacrylat und dem Kohlenwasserstoffpolymer bestehen.

4. System gemäß einem der Ansprüche 1 bis 3 einschließlich, **dadurch gekennzeichnet, dass** das Kohlenwasserstoffpolymer aus der Gruppe ausgewählt ist, die aus Polyethylen, Polystyrol, Polyisobutylen, Polybutadien und dem Copolymer von Polyethylen/-butylen besteht.

5. System gemäß einem der Ansprüche 1 bis 4 einschließlich, **dadurch gekennzeichnet, dass** es sich bei dem Kohlenwasserstoffpolymer um Polyisobutylen handelt.

6. System gemäß den Ansprüchen 1 und 2, **dadurch gekennzeichnet, dass** die Polymere des Gemischs aus dem Polysiloxan und dem Polyacrylat bestehen.

7. System gemäß Anspruch 6, **dadurch gekennzeichnet, dass** das Polyacrylat in einer Menge vorhanden ist, die im Bereich von etwa 2 bis etwa 96 Gew.-% des Systems liegt, und das Polysiloxan in einer Menge vorhanden ist, die im Bereich von etwa 98 bis etwa 4 Gew.-% des Systems liegt.

8. System gemäß Anspruch 6, **dadurch gekennzeichnet, dass** das System, bezogen auf das Gesamtgewicht des Systems, etwa 0,3 bis etwa 50 Gew.-% Albuterol, etwa 14 bis etwa 97 Gew.-% Polysiloxan, etwa 2 bis etwa 85

Gew.-% Polyacrylat, 0 bis etwa 20 Gew.-% Beschleuniger und etwa 0 bis etwa 30 Gew.-% Cosolventien umfasst.

9. System gemäß Anspruch 6, **dadurch gekennzeichnet, dass** das System, bezogen auf das Gesamtgewicht des Systems, etwa 0,3 bis etwa 50 Gew.-% des Wirkstoffs, etwa 14 bis etwa 97 Gew.-% Polysiloxan, etwa 2 bis etwa 85 Gew.-% Polyacrylat, 0 bis etwa 20 Gew.-% Beschleuniger und etwa 0 bis etwa 30 Gew.-% Cosolventien umfasst.

10. System gemäß Anspruch 1, **dadurch gekennzeichnet, dass** das Gemisch noch weitere Polymere enthält.

11. System gemäß einem der Ansprüche 1 bis 10 einschließlich, **dadurch gekennzeichnet, dass** die Zusammensetzung weiterhin einen hydrophilen Füllstoff umfasst.

12. System gemäß Anspruch 11, **dadurch gekennzeichnet, dass** der hydrophile Füllstoff Aluminiumsilicat-Ton enthält.

13. System gemäß einem der Ansprüche 1 bis 12 einschließlich, **dadurch gekennzeichnet, dass** das System weiterhin ein Trägermaterial umfasst, das über eine Oberfläche des Haftklebersystems gelegt ist, wobei das Trägermaterial für den darin enthaltenen Wirkstoff im Wesentlichen undurchlässig ist.

14. System gemäß Anspruch 13, **dadurch gekennzeichnet, dass** das System weiterhin eine Trennschicht umfasst, die über eine Oberfläche des Haftklebersystems gegenüber des Trägers gelegt ist.

15. System gemäß einem der Ansprüche 1 bis 14 einschließlich, **dadurch gekennzeichnet, dass** der Wirkstoff ein Steroid ist.

16. System gemäß Anspruch 15, **dadurch gekennzeichnet, dass** das Steroid ein Estrogen ist, das aus der Gruppe ausgewählt ist, die aus konjugierten Estrogenen, veresterten Estrogenen, Estropipat, 17β-Estradiol, Equilin, Mestranol, Estron, Estriol, Ethinylestradiol und Diethylstilbestrol besteht.

17. System gemäß Anspruch 15, **dadurch gekennzeichnet, dass** das Sterold ein Gestagen ist.

18. System gemäß Anspruch 17, **dadurch gekennzeichnet, dass** das Gestagen aus der Gruppe ausgewählt ist, die aus Progesteron, 19-Norprogesteron, Norethindron, Norethindronacetat, Melengestrol, Chloromadinon, Ethisteron, Medroxyprogesteronacetat, Hydroxyprogesteroncaproat, Ethinodioldiacetat, Norethinodrel, 17α-Hydroxyprogesteron, Dydrogesteron, Dimethisteron, Ethinylestrenol, Demegeston, Promegeston und Megestrolacetat besteht.

19. System gemäß einem der Ansprüche 1 bis 14 einschließlich, **dadurch gekennzeichnet, dass** der Wirkstoff ein β_2-adrenergischer Agonist ist.

20. System gemäß Anspruch 19, **dadurch gekennzeichnet, dass** der β_2-adrenergische Agonist aus der Gruppe ausgewählt ist, die aus Metaproterenol, Terbutalin, Albuterol, Carbuterol, Rimiterol, Salmefamol, Fenoterol, Soterenol, Tratochinol und Chinterenol besteht.

21. System gemäß einem der Ansprüche 1 bis 14 einschließlich, **dadurch gekennzeichnet, dass** der Wirkstoff ein herzaktiver Wirkstoff ist.

22. System gemäß Anspruch 21, **dadurch gekennzeichnet, dass** der herzaktive Wirkstoff aus der Gruppe ausgewählt ist, die aus Nitroglycerin, Isosorbiddinitrat, Isosorbidmononitraten, Chinidinsulfat, Procainamid, Benzydroflumethiazid, Bendroflumethiazid, Chlorothiazid, Nifedipin, Nicardipin, Verapamil, Diltiazem, Timolol, Propanolol, Captopril, Clonidin und Prazosin besteht.

23. System gemäß einem der Ansprüche 1 bis 14 einschließlich, **dadurch gekennzeichnet, dass** der Wirkstoff ein cholinergischer Agonist ist.

24. System gemäß Anspruch 23, **dadurch gekennzeichnet, dass** der cholinergische Agonist aus der Gruppe ausgewählt ist, die aus Cholin, Acetylcholin, Methacholin, Carbachol, Bethanechol, Pilocarpin, Muscarin und Arecolin besteht.

25. System gemäß einem der Ansprüche 1 bis 24 einschließlich, **dadurch gekennzeichnet, dass** der Wirkstoff mit dem Gemisch innig gemischt wird.

26. System gemäß einem der Ansprüche 1 bis 25 einschließlich, **dadurch gekennzeichnet, dass** das Polyacrylat wenigstens 50 Gew.-% eines Acrylats oder Alkylacrylatmonomers umfasst.

27. System gemäß Anspruch 16, **dadurch gekennzeichnet, dass** es sich bei dem Estrogen um 17β-Estradiol handelt und das 17β-Estradiol in dem System in einer Menge von etwa 1 bis etwa 5 Gew.-% vorhanden ist.

28. System gemäß Anspruch 18, **dadurch gekennzeichnet, dass** es sich bei dem Gestagen um Norethindronacetat handelt und das Norethindronacetat in dem System in einer Menge von etwa 1 bis etwa 5 Gew.-% vorhanden ist.

29. System gemäß Anspruch 20, **dadurch gekennzeichnet, dass** es sich bei dem β_2-adrenergischen Agonisten um Albuterol handelt und das Albuterol in dem System in einer Menge von weniger als etwa 30 Gew.-% vorhanden ist.

30. System gemäß Anspruch 22, **dadurch gekennzeichnet, dass** es sich bei dem herzaktiven Mittel um Nitroglycerin handelt und das Nitroglycerin in dem System in einer Menge von weniger als etwa 25 Gew.-% vorhanden ist.

31. System gemäß Anspruch 23, **dadurch gekennzeichnet, dass** es sich bei dem cholinergischen Agonisten um Pilocarpin handelt und das Pilocarpin in dem System in einer Menge von weniger als etwa 30 Gew.-% vorhanden ist.

32. System gemäß einem der Ansprüche 1 bis 14 einschließlich, **dadurch gekennzeichnet, dass** der Wirkstoff ein Tranquilizer ist.

33. System gemäß Anspruch 32, **dadurch gekennzeichnet, dass** der Tranquilizer aus der Gruppe ausgewählt ist, die aus Alprazolam, Chlordiazepoxid, Chlorazeptat, Halazepam, Oxazepam, Prazepam, Clonazepam, Flurazepam, Triazolam, Lorazepam und Diazepam besteht.

34. System gemäß Anspruch 32, **dadurch gekennzeichnet, dass** es sich bei dem Tranquilizer um Alprazolam handelt.

35. System gemäß einem der Ansprüche 1 bis 14 einschließlich, **dadurch gekennzeichnet, dass** der Wirkstoff ein Antipsychotikum ist.

36. System gemäß Anspruch 35, **dadurch gekennzeichnet, dass** das Antipsychotikum aus der Gruppe ausgewählt ist, die aus Thiopropazat, Chlorpromazin, Triflupromazin, Mesoridazin, Piperacetazin, Thioridazin, Acetophenazin, Fluphenazin, Perphenazin, Trifluoperazin, Chlorprathixen, Thiothixen. Haloperidol, Bromperidol, Loxapin und Molindon besteht.

37. System gemäß Anspruch 36, **dadurch gekennzeichnet, dass** es sich bei dem Antipsychotikum um Haloperidol handelt.

38. System gemäß einem der Ansprüche 1 bis 14 einschließlich, **dadurch gekennzeichnet, dass** der Wirkstoff ein Anästhetikum ist.

39. System gemäß Anspruch 38, **dadurch gekennzeichnet, dass** das Anästhetikum aus der Gruppe ausgewählt ist, die aus Lidocain, Tetracain, Dyclonin, Dibucain, Cocain, Procain, Mepivacain, Bupivacain, Etidocain, Prilocain und Benzocain besteht.

40. System gemäß Anspruch 39, **dadurch gekennzeichnet, dass** es sich bei dem Anästhetikum um Lidocain handelt.

41. System gemäß einem der Ansprüche 1 bis 14 einschließlich, **dadurch gekennzeichnet, dass** der Wirkstoff ein Analgetikum ist.

42. System gemäß Anspruch 41, **dadurch gekennzeichnet, dass** das Analgetikum aus der Gruppe ausgewählt ist, die aus Fentanyl, Buprenorphin und Codein besteht.

43. System gemäß einem der Ansprüche 1 bis 14 einschließlich, **dadurch gekennzeichnet, dass** der Wirkstoff eine Wirkung auf das Zentralnervensystem hat.

44. System gemäß Anspruch 43, **dadurch gekennzeichnet, dass** es sich bei dem Wirkstoff um Nicotin handelt.

45. System gemäß einem der Ansprüche 1 bis 14 einschließlich, **dadurch gekennzeichnet, dass** die Zusammensetzung ein Gemisch aus wenigstens zwei Wirkstoffen enthält.

46. System gemäß Anspruch 45, **dadurch gekennzeichnet, dass** die wenigstens zwei Wirkstoffe ein Gestagen und ein Estrogen umfassen.

47. System gemäß Anspruch 46, **dadurch gekennzeichnet, dass** das Gestagen aus der Gruppe ausgewählt ist, die aus Progesteron, 19-Norprogesteron, Norethindron, Norethindronacetat, Melengesterol, Chloromadinon, Ethisteron, Medroxyprogesteronacetat, Hydroxyprogesteroncaproat, Ethinodioldiacetat, Norethinodrel, 17α-Hydroxyprogesteron, Dydrogesteron, Dimethisteron, Ethinylestrenol, Norgestrel, Demegeston, Promegeston und Megestrolacetat besteht.

48. System gemäß Anspruch 47, **dadurch gekennzeichnet, dass** es sich bei dem Gestagen um Norethindronacetat handelt.

49. System gemäß Anspruch 47, **dadurch gekennzeichnet, dass** das Estrogen aus der Gruppe ausgewählt ist, die aus konjugierten Estrogenen, veresterten Estrogenen, Estropipat, 17β-Estradiol, Equilin, Mestranol, Estron, Estriol, Ethinylestradiol und Diethylstilbestrol besteht.

50. System gemäß Anspruch 49, **dadurch gekennzeichnet, dass** es sich bei dem Estrogen um 17β-Estradiol handelt.

51. System gemäß einem der Ansprüche 1 bis 6 und 10 bis 14, **dadurch gekennzeichnet, dass** das System eine erhöhte Permeationsrate des Wirkstoffs durch die Dermis eines Patienten erreicht im Vergleich zur Permeationsrate, die mit einem System erreicht wird, das entweder das Polyacrylat oder das zweite Polymer als einziges Polymer umfasst.

52. System gemäß einem der Ansprüche 1 bis 6 und 10 bis 14 einschließlich, **dadurch gekennzeichnet, dass** das System eine verringerte Permeationsrate des Wirkstoffs durch die Dermis eines Patienten erreicht im Vergleich zur Permeationsrate, die mit einem System erreicht wird, das entweder das Polyacrylat oder das zweite Polymer als einziges Polymer umfasst.

53. System gemäß einem der Ansprüche 1 bis 7, **dadurch gekennzeichnet, dass** die Zusammensetzung weiterhin ein Additiv umfasst, das aus der Gruppe ausgewählt ist, die aus einem Beschleuniger, einem Füllstoff, einem Cosolvens und einem Exzipienten besteht.

54. System gemäß einem der Ansprüche 1 bis 53 einschließlich, **dadurch gekennzeichnet, dass** das Polyacrylat und das zweite Polymer Haftkleber sind.

55. Haftklebendes transdermales Wirkstoffabgabesystem gemäß Anspruch 1, **dadurch gekennzeichnet, dass** die dermale Haftkleberzusammensetzung ein Gemisch umfasst aus:

(a) zwei Polymeren, die im Wesentlichen aus etwa 2 bis etwa 96 Gew.-% eines Polyacrylats und etwa 98 bis etwa 4 Gew.-% eines Polysiloxans besteht, wobei die beiden Polymere in einer Menge von etwa 99 bis etwa 50 Gew.-% des Systems vorhanden sind;

(b) einem Wirkstoff in einer Menge von etwa 0,3 bis etwa 50 Gew.-% des Systems;

(c) einer wirksamen Menge eines Cosolvens für den Wirkstoff, wobei die Menge bis zu etwa 30 Gew.-% des Systems beträgt; und

(d) einer wirksamen Menge eines Beschleunigers, wobei die Menge bis zu etwa 20 Gew.-% des Systems beträgt.

56. System gemäß Anspruch 55, **dadurch gekennzeichnet, dass** die Zusammensetzung weiterhin Füllstoffe und Exzipienten in einer Menge von etwa 1 bis etwa 15 Gew.-% des dermalen Klebersystems umfasst.

57. Haftklebendes transdermales Wirkstoffabgabesystem gemäß Anspruch 1, **dadurch gekennzeichnet, dass** die dermale Haftkleberzusammensetzung ein Gemisch umfasst aus:

(a) einem Polyacrylat, das einen ersten Löslichkeitsparameter aufweist, und einem zweiten Polymer, das aus der Gruppe ausgewählt ist, die aus einem Polysiloxan und Kohlenwasserstoffpolymeren mit einem zweiten Löslichkeitsparameter besteht, wobei der erste und der zweite Löslichkeitsparameter um einen Betrag von wenigstens 4 $(J/cm^3)^{1/2}$ voneinander verschieden sind; und

(b) einer therapeutisch wirksamen Menge eines Wirkstoffs für die transdermale Verabreichung;

wobei das Polyacrylat und das zweite Polymer die Permeationsrate des Wirkstoffs durch die Dermis modulieren und wobei das System kein Ethylen/Vinylacetat-Copolymer enthält.

58. Haftklebendes transdermales Wirkstoffabgabesystem gemäß Anspruch 1, **dadurch gekennzeichnet, dass** die dermale Haftkleberzusammensetzung ein Gemisch umfasst aus:

(a) einem Polyacrylat und einem zweiten Polymer, das aus der Gruppe ausgewählt ist, die aus Polytetrafluorethylen, Polyvinylchlorid, Polyvinylidenchlorid, Polychloropren, Polyacrylnitril, Nylon-6,6, Epoxidharz und einem Copolymer von Polybutadien/Acrylnitril besteht; und

(b) einer therapeutisch wirksamen Menge eines Wirkstoffs für die transdermale Verabreichung;

wobei das Polyacrylat und das zweite Polymer die Permeationsrate des Wirkstoffs durch die Dermis modulieren und wobei das System kein Ethylen/Vinylacetat-Copolymere enthält.

59. Verfahren zum Modulieren der Abgabegeschwindigkeit eines Wirkstoffs durch ein transdermales Wirkstoffabgabesystem, das eine Haftkleberzusammensetzung umfasst, in die ein Wirkstoff eingebaut ist, **dadurch gekennzeichnet, dass** das Verfahren die folgenden Schritte umfasst:

a) Auswählen von zwei oder mehr im Wesentlichen unmischbaren oder unlöslichen polymeren Materialien als Komponenten eines mehrfachen Polymerklebersystems, so dass das System einen Nettolöslichkeitsparameter hat, der zu einer modifizierten Löslichkeit eines Wirkstoffs in der Zusammensetzung führt; und

b) Kombinieren der zwei oder mehr polymeren Materialien mit einem Wirkstoff unter Bildung eines Haftklebermatrixsystems, wobei das Matrixsystem eine Wirkstoffabgaberate erreicht, die durch den Nettolöslichkeitsparameter bestimmt wird und die sich von der Abgaberate unterscheidet, die mit einem Haftklebermatrixsystem erreicht wird, das nur eins der wenigstens zwei polymeren Materialien als einziges polymeres Material umfasst.

60. Verfahren gemäß Anspruch 59, **dadurch gekennzeichnet, dass** der Wirkstoff mit den zwei oder mehr Polymeren in der Haftklebermatrix innig gemischt wird.

61. Verfahren gemäß Anspruch 60, **dadurch gekennzeichnet, dass** der Schritt des Auswählens den Schritt des Messens der Flussrate aus verschiedenen Gewichtsverhältnissen der ausgewählten zwei oder mehr Polymere und des Wählens des Verhältnisses, das eine vorgewählte Flussrate ergibt, umfasst.

Revendications

1. Un système d'administration transdermique de médicament, sensible à la pression, comprenant une composition dermique adhésive sensible à la pression dans laquelle est incorporé un médicament, **caractérisé en ce que** la composition dermique adhésive sensible à la pression comprend un mélange de :

(a) un polyacrylate ayant une première solubilité et un second polymère ayant une seconde solubilité choisi dans la classe formée par un polysiloxane et un polymère hydrocarboné ; et

(b) une quantité à effet thérapeutique d'un médicament pour administration transdermique,

dans lequel le polyacrylate et le second polymère modulent la vitesse de perméation du médicament à travers le derme par ajustement de la solubilité du médicament dans le système, et dans lequel la composition exclut les polymères d'éthylène et d'acétate de vinyle.

2. Le système de la revendication 1, **caractérisé en ce que** les polymères du mélange consistent en le polyacrylate et le second polymère.

3. Le système tel que revendiqué dans les revendications 1 et 2, **caractérisé en ce que** les polymères du mélange consistent en le polyacrylate et le polymère hydrocarboné.

4. Le système tel que revendiqué dans l'une quelconque des revendications 1 à 3 inclusivement, **caractérisé en ce que** le polymère hydrocarboné est choisi dans la classe formée par le polyéthylène, le polystyrène, le polyisobutylène, le polybutadiène et le copolymère de polyéthylène/butylène.

5. Le système tel que revendiqué dans l'une quelconque des revendications 1 à 4 inclusivement, **caractérisé en ce que** le polymère hydrocarboné est le polyisobutylène.

6. Le système des revendications 1 et 2, **caractérisé en ce que** les polymères du mélange consistent en le polysiloxane et le polyacrylate.

7. Le système de la revendication 6, **caractérisé en ce que** le polyacrylate est présent en une quantité comprise entre environ 2 % et environ 96 % en poids du système et le polysiloxane est présent en une quantité comprise entre environ 98 % et environ 4 % en poids du système.

8. Le système de la revendication 6, **caractérisé en ce que** le système comprend, par rapport au poids total du système, environ 0,3 à environ 50 % en poids d'albutérol, environ 14 à environ 97 % en poids de polysiloxane, environ 2 à environ 85 % en poids de polyacrylate, 0 à environ 20 % en poids d'activateurs, et environ 0 à environ 30 % en poids de co-solvants.

9. Le système de la revendication 6, **caractérisé en ce que** le système comprend, par rapport au poids total du système, environ 0,3 à environ 50 % en poids dudit médicament, environ 14 à environ 97 % en poids de polysiloxane, environ 2 à environ 85 % en poids de polyacrylate, 0 à environ 20 % en poids d'activateurs, et environ 0 à environ 30 % en poids de co-solvants.

10. Le système de la revendication 1, **caractérisé en ce que** le mélange comprend des polymères supplémentaires.

11. Le système de l'une quelconque des revendications 1 à 10 inclusivement, **caractérisé en ce que** la composition comprend, de plus, une charge hydrophile.

12. Le système de la revendication 11, **caractérisé en ce que** la charge hydrophile comprend une argile du type aluminosilicate.

13. Le système de l'une quelconque des revendications 1 à 12 inclusivement, **caractérisé en ce que** le système comprend, de plus, un matériau de support superposé à une surface du système adhésif sensible à la pression, ledit matériau de support étant sensiblement imperméable au médicament contenu dans ce système.

14. Le système de la revendication 13, **caractérisé en ce que** le système comprend, de plus, une feuille détachable superposée à une surface du système adhésif sensible à la pression qui est opposée audit matériau de support.

15. Le système de l'une quelconque des revendications 1 à 14 inclusivement, **caractérisé en ce que** le médicament est un stéroïde.

16. Le système de la revendication 15, **caractérisé en ce que** le stéroïde est un oestrogène choisi dans la classe formée par les oestrogènes conjugués, les oestrogènes estérifiés, l'oestropipate, le 17β-oestradiol, l'équiline, le mestranol, l'oestrone, l'oestriol, l'éthinyl-oestradiol et le diéthylstilbestrol.

17. Le système de la revendication 15, **caractérisé en ce que** le stéroïde est un agent progestatif.

18. Le système de la revendication 17, **caractérisé en ce que** l'agent progestatif est choisi dans la classe formée par la progestérone, la 19-norprogestérone, la noréthindrone, l'acétate de noréthindrone, le mélengestrol, la chlormadinone, l'éthistérone, l'acétate de médroxyprogestérone, le caproate d'hydroxyprogestérone, le diacétate d'éthynodiol, le noréthynodrel, la 17α-hydroxyprogestérone, la dydrogestérone, la diméthistérone, le lynestrénol, la démégestone, la promégestone et l'acétate de mégestrol.

19. Le système de l'une quelconque des revendications 1 à 14 inclusivement, **caractérisé en ce que** le médicament est un agoniste β_2-adrénergique.

20. Le système de la revendication 19, **caractérisé en ce que** l'agoniste β_2-adrénergique est choisi dans la classe formée par le métaprotérénol, la terbutaline, l'albutérol, le carbutérol, le rimitérol, le salméfamol, le fénotérol, le sotérénol, le tratoquinol et le quintérénol.

21. Le système de l'une quelconque des revendications 1 à 14 inclusivement, **caractérisé en ce que** le médicament est un médicament cardio-actif.

22. Le système de la revendication 21, **caractérisé en ce que** ledit agent cardio-actif est choisi dans la classe formée par la nitroglycérine, le dinitrate d'isosorbide, les mononitrates d'isosorbide, le sulfate de quinidine, le procaïnamide, le benzydrofluméthiazide, le bendrofluméthiazide, le chlorothiazide, la nifédipine, la nicardipine, le vérapamil, le diltiazem, le thimolol, le propranolol, le captopril, la clonidine et la prazosine.

23. Le système de l'une quelconque des revendications 1 à 14 inclusivement, **caractérisé en ce que** le médicament est un agoniste cholinergique.

24. Le système de la revendication 23, **caractérisé en ce que** l'agoniste cholinergique est choisi dans la classe formée par la choline, l'acétylcholine, la méthacholine, le carbachol, le béthanechol, la pilocarpine, la muscarine et l'arécoline.

25. Le système de l'une quelconque des revendications 1 à 24 inclusivement, **caractérisé en ce que** le médicament est mélangé intimement avec le mélange.

26. Le système de l'une quelconque des revendications 1 à 25 inclusivement, **caractérisé en ce que** le polyacrylate comprend au moins 50 % en poids d'un monomère acrylique ou acrylate d'alkyle.

27. Le système de la revendication 16, **caractérisé en ce que** l'oestrogène est le 17β-oestradiol et le 17β-oestradiol est présent dans le système en une quantité d'environ 1 % à environ 5 % en poids.

28. Le système de la revendication 18, **caractérisé en ce que** l'agent progestatif est l'acétate de noréthindrone et l'acétate de noréthindrone est présent dans le système en une quantité d'environ 1 % à environ 5 % en poids.

29. Le système de la revendication 20, **caractérisé en ce que** l'agoniste β_2-adrénergique est l'albutérol et l'albutérol est présent dans le système en une quantité inférieure à environ 30 % en poids.

30. Le système de la revendication 22, **caractérisé en ce que** l'agent cardio-actif est la nitroglycérine et la nitroglycérine est présente dans le système en une quantité inférieure à environ 25 % en poids.

31. Le système de la revendication 23, **caractérisé en ce que** l'agoniste cholinergique est la pilocarpine et la pilocarpine est présente dans le système en une quantité inférieure à environ 30 % en poids.

32. Le système de l'une quelconque des revendications 1 à 14 inclusivement, **caractérisé en ce que** le médicament est un tranquillisant.

33. Le système de la revendication 32, **caractérisé en ce que** le tranquillisant est choisi dans la classe formée par l'alprazolam, le chlordiazépoxyde, le clorazepate, l'halazépam, l'oxazépam, le prazépam, le clonazépam, le flurazépam, le triazolam, le lorazépam et le diazépam.

34. Le système de la revendication 33, **caractérisé en ce que** le tranquillisant est l'alprazolam.

35. Le système de l'une quelconque des revendications 1 à 14 inclusivement, **caractérisé en ce que** le médicament est un antipsychotique.

36. Le système de la revendication 35, **caractérisé en ce que** l'antipsychotique est choisi dans la classe formée par le thiopropazate, la chlorpromazine, la triflupromazine, la mésoridazine, la pipéracétazine, la thioridazine, l'acétophénazine, la fluphénazine, la perphénazine, la trifluopérazine, le chlorprathixène, le thiothixène, l'halopéridol, le brompéridol, la loxapine et la molindone.

37. Le système de la revendication 36, **caractérisé en ce que** l'antipsychotique est l'halopéridol.

38. Le système de l'une quelconque des revendications 1 à 14 inclusivement, **caractérisé en ce que** le médicament est un anesthésique.

39. Le système de la revendication 38, **caractérisé en ce que** l'anesthésique est choisi dans la classe formée par la lidocaine, la tétracaïne, la dyclonine, la dibucaïne, la cocaïne, la procaïne, la mépivacaïne, la bupivacaïne, l'étidocaïne, la prilocaïne et la benzocaïne.

40. Le système de la revendication 39, **caractérisé en ce que** l'anesthésique est la lidocaïne.

41. Le système de l'une quelconque des revendications 1 à 14 inclusivement, **caractérisé en ce que** le médicament est un analgésique.

42. Le système de la revendication 41, **caractérisé en ce que** l'analgésique est choisi dans la classe formée par le fentanyl, la buprénorphine et la codéine.

43. Le système de l'une quelconque des revendications 1 à 14 inclusivement, **caractérisé en ce que** le médicament a une action sur le système nerveux central.

44. Le système de la revendication 43, **caractérisé en ce que** le médicament est la nicotine.

45. Le système de l'une quelconque des revendications 1 à 14 inclusivement, **caractérisé en ce que** la composition comprend un mélange d'au moins deux médicaments.

46. Le système de la revendication 45, **caractérisé en ce que** les deux médicaments au moins comprennent un agent progestatif et un oestrogène.

47. Le système de la revendication 46, **caractérisé en ce que** ledit agent progestatif est choisi dans la classe formée par la progestérone, la 19-norprogestérone, la noréthindrone, l'acétate de noréthindrone, le mélengestrol, la chlormadinone, l'éthistérone, l'acétate de médroxyprogestérone, le caproate d'hydroxyprogestérone, le diacétate d'éthynodiol, le noréthynodrel, la 17α-hydroxyprogestérone, la dydrogestérone, la diméthistérone, le lynestrénol, le norgestrel, la démégestone, la promégestone et l'acétate de mégestrol.

48. Le système de la revendication 47, **caractérisé en ce que** ledit agent progestatif est l'acétate de noréthindrone.

49. Le système de la revendication 47, **caractérisé en ce que** ledit oestrogène est choisi dans la classe formée par les oestrogènes conjugués, les oestrogènes estérifiés, l'oestropipate, le 17β-oestradiol, l'équiline, le mestranol, l'oestrone, l'oestriol, l'éthinyl-oestradiol et le diéthylstilbestrol.

50. Le système de la revendication 49, **caractérisé en ce que** ledit oestrogène est le 17β-oestradiol.

51. Le système de l'une quelconque des revendications 1 à 6 et 10 à 14, **caractérisé en ce que** ledit système atteint une plus grande vitesse de perméation du médicament à travers le derme d'un sujet que la vitesse de perméation atteinte par un système comprenant l'un dudit polyacrylate ou dudit second polymère comme seul polymère.

52. Le système de l'une quelconque des revendications 1 à 6 et 10 à 14 inclusivement, **caractérisé en ce que** ledit système atteint une plus basse vitesse de perméation du médicament à travers le derme d'un sujet que la vitesse

de perméation atteinte par un système comprenant ledit polyacrylate ou ledit second polymère comme seul polymère.

53. Le système de l'une quelconque des revendications 1 à 7, **caractérisé en ce que** la composition comprend, de plus, un additif choisi dans la classe formée par un activateur, une charge, un co-solvant et un excipient.

54. Le système de l'une quelconque des revendications 1 à 53 inclusivement, **caractérisé en ce que** le polyacrylate et le second polymère sont des adhésifs sensibles à la pression.

55. Un système d'administration transdermique de médicament, sensible à la pression, tel que revendiqué dans la revendication 1, **caractérisé en ce que** la composition dermique adhésive sensible à la pression comprend un mélange de :

(a) deux polymères consistant essentiellement en environ 2 % à environ 96 % en poids d'un polyacrylate et environ 98 % à environ 4 % en poids d'un polysiloxane, les deux polymères étant présents en une quantité d'environ 99 % à environ 50 % en poids dudit système ;
(b) un médicament en une quantité d'environ 0,3 % à environ 50 % en poids dudit système ;
(c) une quantité efficace d'un co-solvant pour le médicament, ladite quantité étant d'au plus environ 30 % en poids dudit système ; et
(d) une quantité efficace d'un activateur, ladite quantité étant d'au plus environ 20 % en poids dudit système.

56. Le système de la revendication 55, **caractérisé en ce que** la composition comprend, de plus, des charges et excipients en une quantité d'environ 1 % à environ 15 % en poids du système adhésif dermique.

57. Un système d'administration transdermique de médicament, sensible à la pression, tel que revendiqué dans la revendication 1, **caractérisé en ce que** la composition dermique adhésive sensible à la pression comprend un mélange de :

(a) un polyacrylate ayant un premier paramètre de solubilité et un second polymère choisi dans la classe formée par un polysiloxane et les polymères hydrocarbonés ayant un second paramètre de solubilité, les premier et second paramètres de solubilité différant l'un de l'autre d'un incrément d'au moins 4 $(J/cm^3)^{1/2}$; et
(b) une quantité à effet thérapeutique d'un médicament pour administration transdermique,

dans lequel le polyacrylate et le second polymère modulent la vitesse de perméation du médicament à travers le derme, et dans lequel le système exclut les copolymères éthylène/acétate de vinyle.

58. Un système d'administration transdermique de médicament, sensible à la pression, tel que revendiqué dans la revendication 1, **caractérisé en ce que** la composition dermique adhésive sensible à la pression comprend un mélange de :

(a) un polyacrylate et un second polymère choisi dans la classe formée par le polytétrafluoréthylène, le chlorure de polyvinyle, le chlorure de polyvinylidène, le polychloroprène, le polyacrylonitrile, le nylon-6,6, une résine époxy et un copolymère polybutadiène/acrylonitrile ; et
(b) une quantité à effet thérapeutique d'un médicament pour administration transdermique,

dans lequel le polyacrylate et le second polymère modulent la vitesse de perméation du médicament à travers le derme, et dans lequel le système exclut un copolymère éthylène/acétate de vinyle.

59. Un procédé pour moduler la vitesse d'administration d'un médicament à partir d'un système d'administration transdermique de médicament comprenant une composition adhésive sensible à la pression dans laquelle est incorporé un médicament, **caractérisé en ce que** le procédé comprend les étapes suivantes :

a) sélectionner deux ou plusieurs matières polymères essentiellement insolubles ou non miscibles comme composants d'un système adhésif à polymères multiples, de sorte que le système ait un paramètre de solubilité global qui donne lieu à une solubilité modifiée d'un médicament dans la composition ; et
b) associer lesdites deux ou plusieurs matières polymères avec un médicament pour former un système à matrice adhésive sensible à la pression, le système à matrice atteignant une vitesse d'administration de médicament qui est déterminée par ledit paramètre de solubilité global et qui diffère de la vitesse d'administration

atteinte par un système à matrice adhésive sensible à la pression comprenant une seule desdites deux ou plusieurs matières polymères comme seule matière polymère.

60. Le procédé de la revendication 59, **caractérisé en ce que** le médicament est intimement mélangé avec les deux ou plusieurs polymères dans la matrice adhésive sensible à la pression.

61. Le procédé de la revendication 60, **caractérisé en ce que** ladite étape de sélection comprend l'étape consistant à mesurer le flux pour divers rapports en poids desdits deux ou plusieurs polymères sélectionnés et choisir le rapport produisant un flux préalablement choisi.

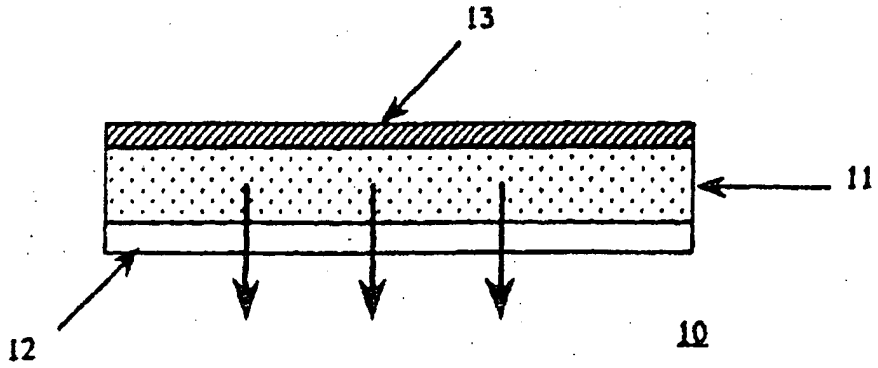

FIG. 1

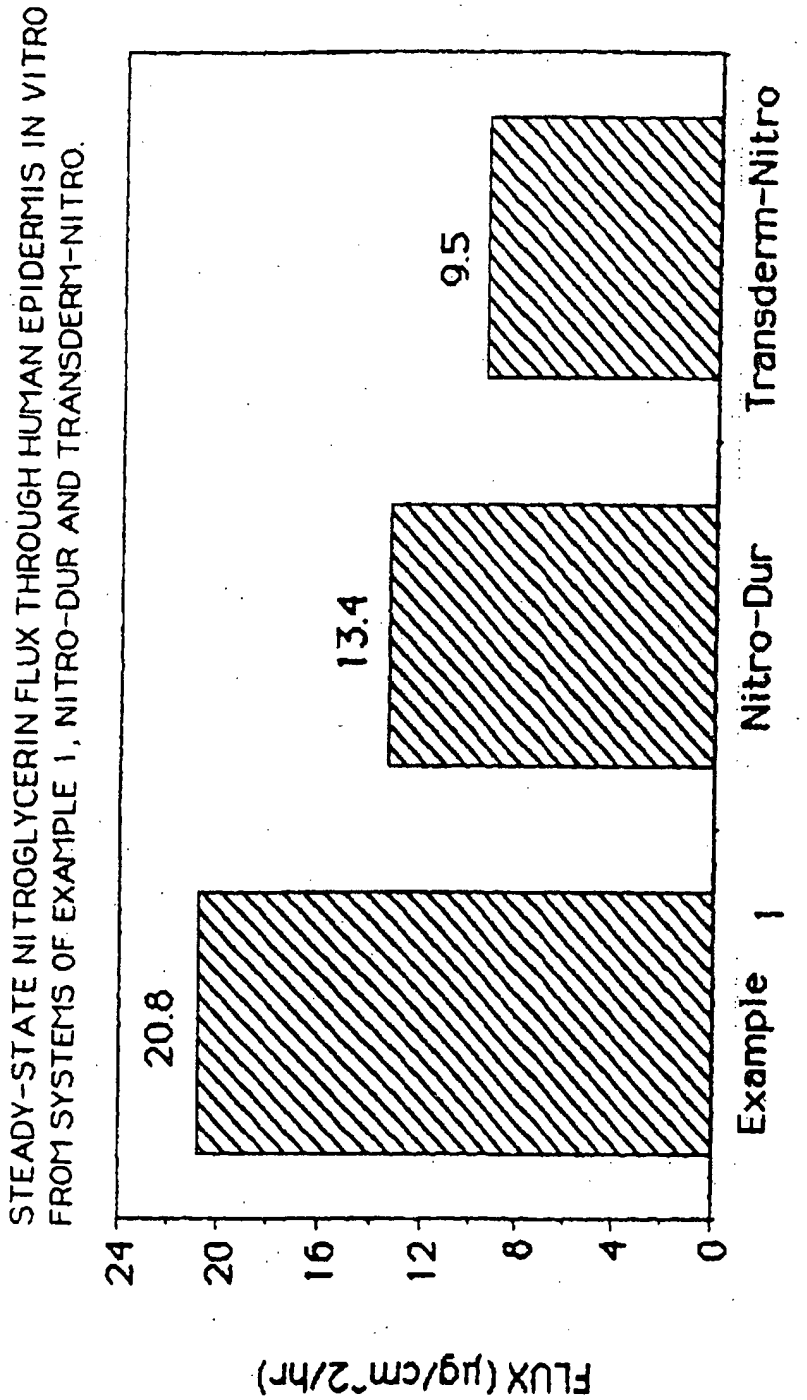
STEADY-STATE NITROGLYCERIN FLUX THROUGH HUMAN EPIDERMIS IN VITRO
FROM SYSTEMS OF EXAMPLE 1, NITRO-DUR AND TRANSDERM-NITRO.
FLUX (µg/cm^2/hr)
24
20
16
12
8
4
0
20.8
13.4
9.5
Example 1
Nitro-Dur
Transderm-Nitro
Product

FIG. 2

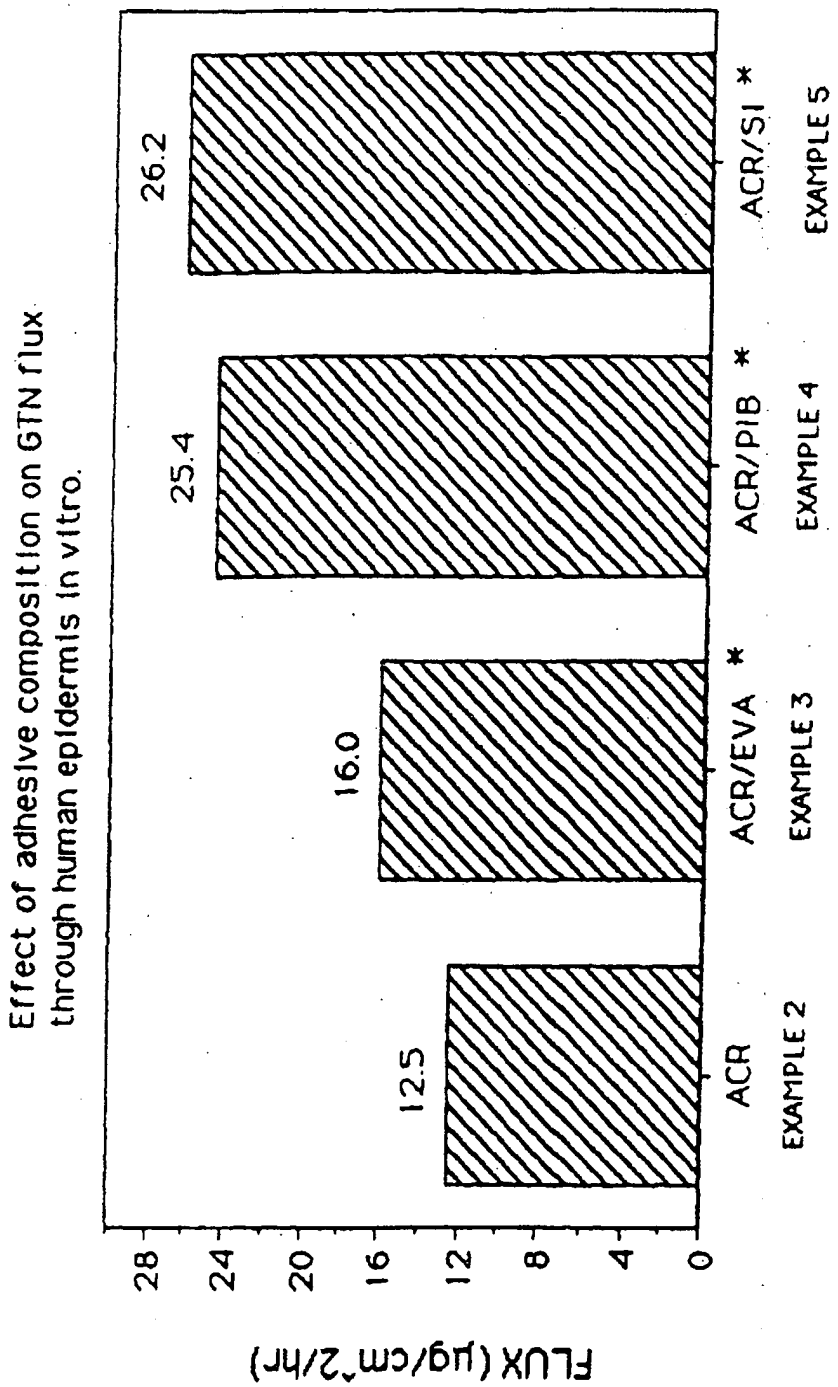

FIG. 3

*ACR/POLYMER ratios of 45/55, w/w.

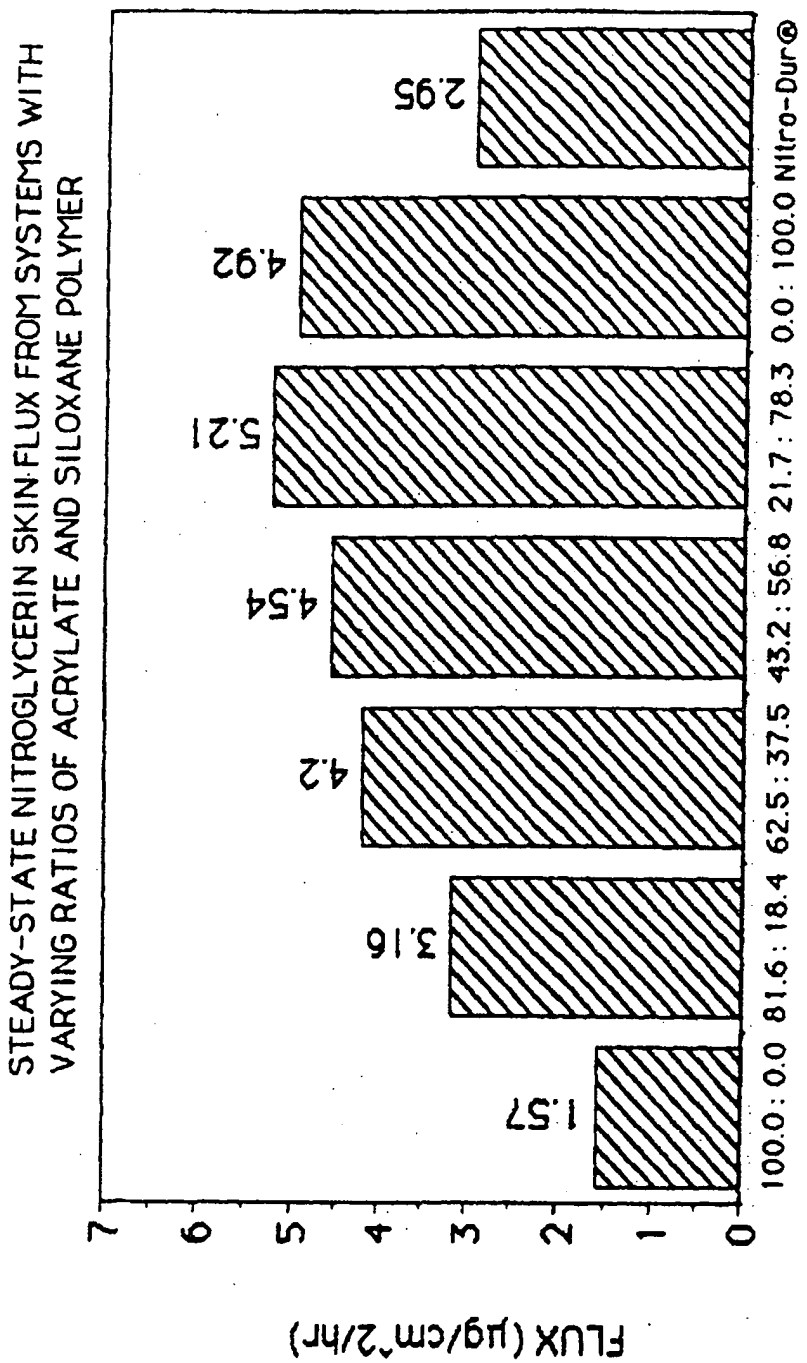
STEADY-STATE NITROGLYCERIN SKIN FLUX FROM SYSTEMS WITH VARYING RATIOS OF ACRYLATE AND SILOXANE POLYMER
FLUX (µg/cm^2/hr)
0
1
2
3
4
5
6
7
1.57
3.16
4.2
4.54
5.21
4.92
2.95
100.0 : 0.0
81.6 : 18.4
62.5 : 37.5
43.2 : 56.8
21.7 : 78.3
0.0 : 100.0 Nitro-Dur®
ACRYLIC:SILOXANE POLYMER RATIO (W/W)

FIG. 4

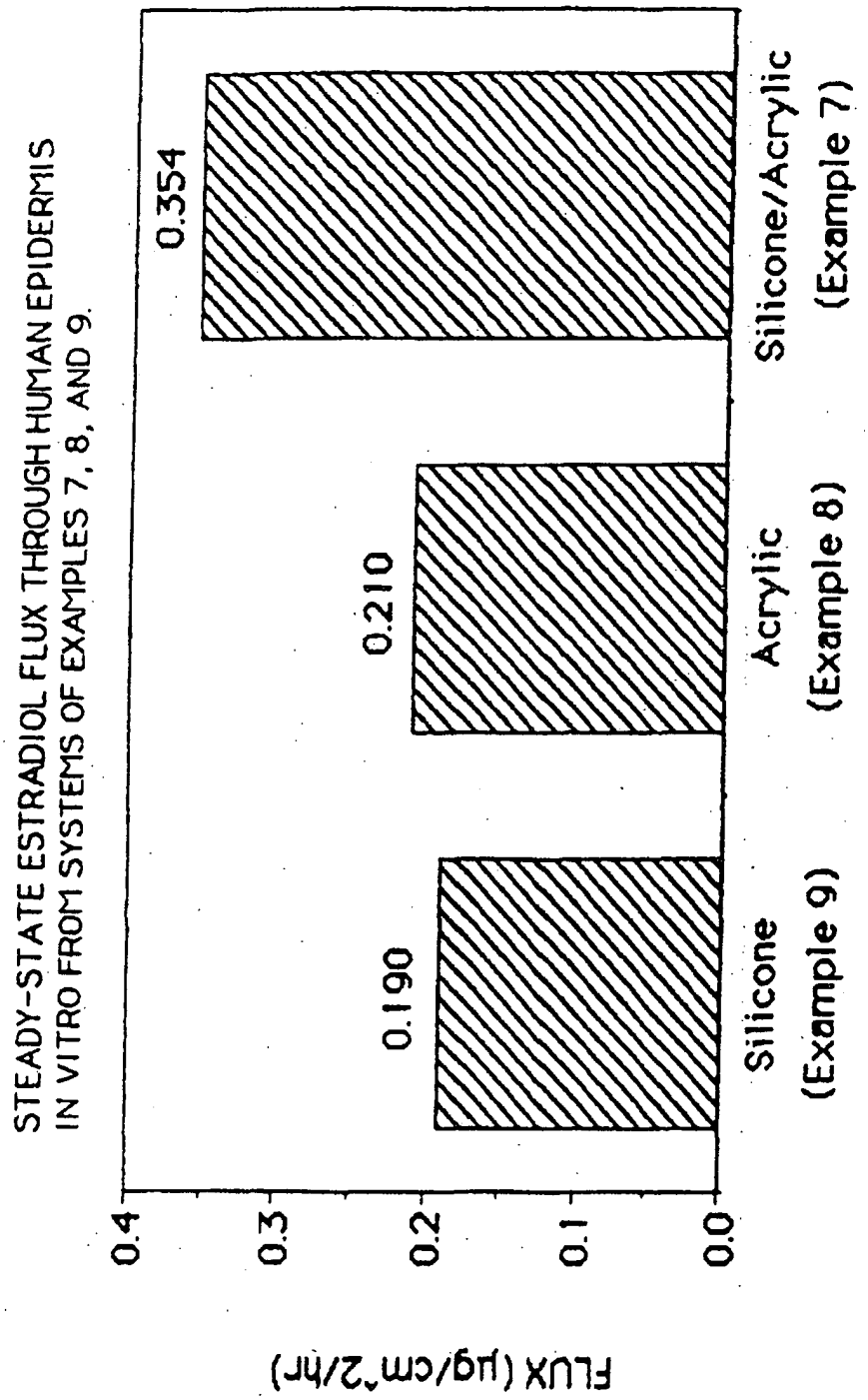
STEADY-STATE ESTRADIOL FLUX THROUGH HUMAN EPIDERMIS
IN VITRO FROM SYSTEMS OF EXAMPLES 7, 8, AND 9.
FLUX (μg/cm^2/hr)
0.4
0.3
0.2
0.1
0.0
0.190
0.210
0.354
Silicone (Example 9)
Acrylic (Example 8)
Silicone/Acrylic (Example 7)

FIG. 5

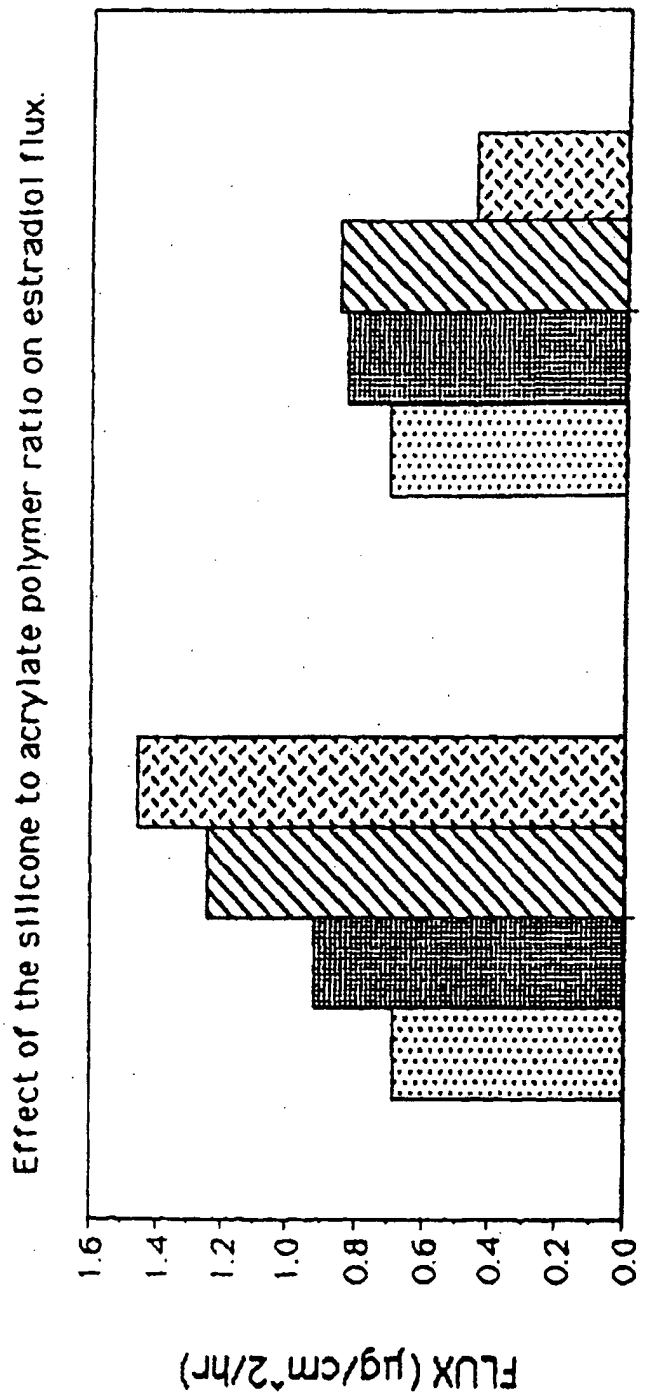
Effect of the silicone to acrylate polymer ratio on estradiol flux.
FLUX (µg/cm^2/hr)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0-22 HR
22-99 HR
STUDY TIME
EX. 10
EX. 11
EX. 12
EX. 13

FIG. 6

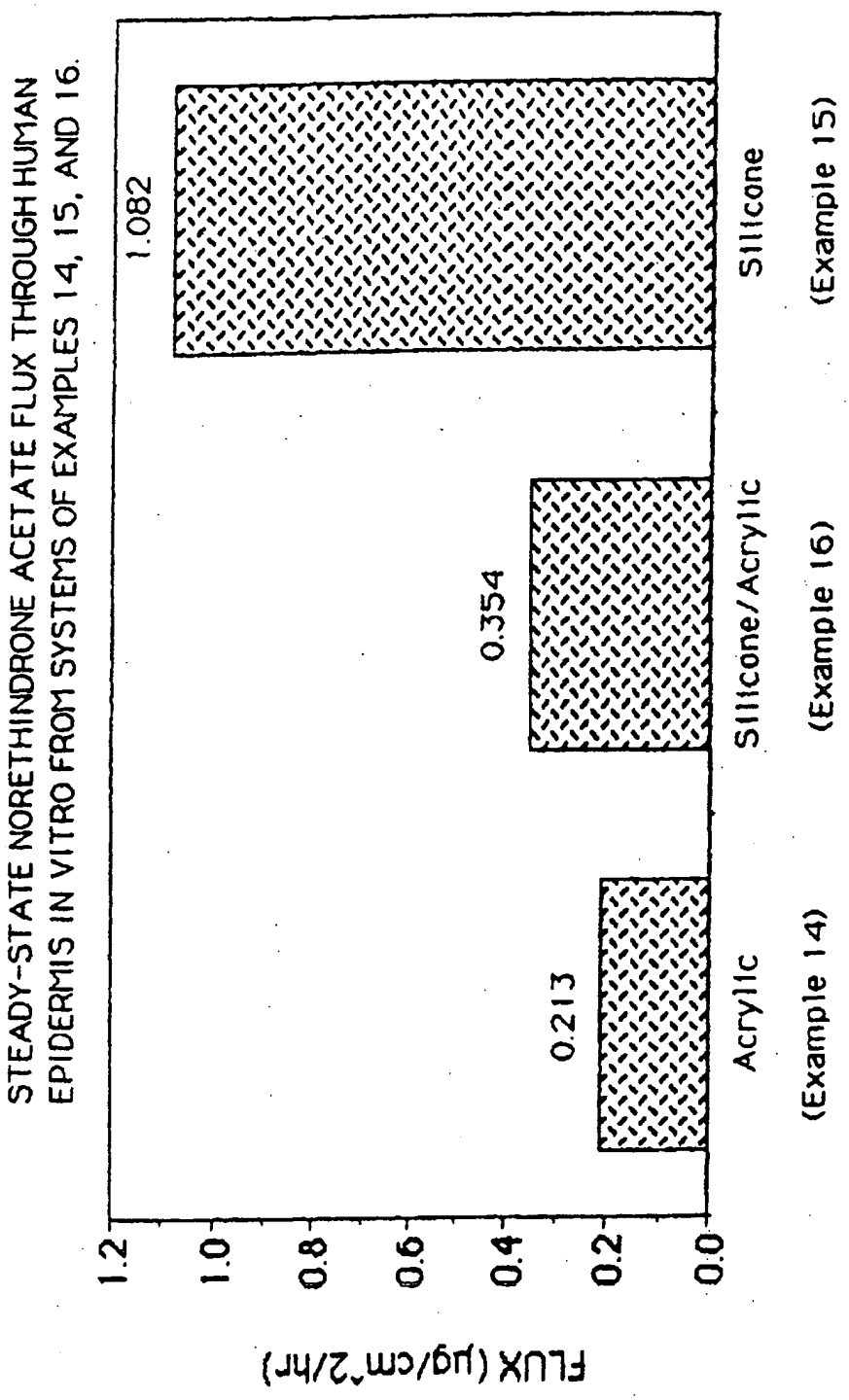
STEADY-STATE NORETHINDRONE ACETATE FLUX THROUGH HUMAN EPIDERMIS IN VITRO FROM SYSTEMS OF EXAMPLES 14, 15, AND 16.
FLUX (μg/cm^2/hr)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.213
0.354
1.082
Acrylic
Silicone/Acrylic
Silicone
(Example 14)
(Example 16)
(Example 15)

FIG. 7

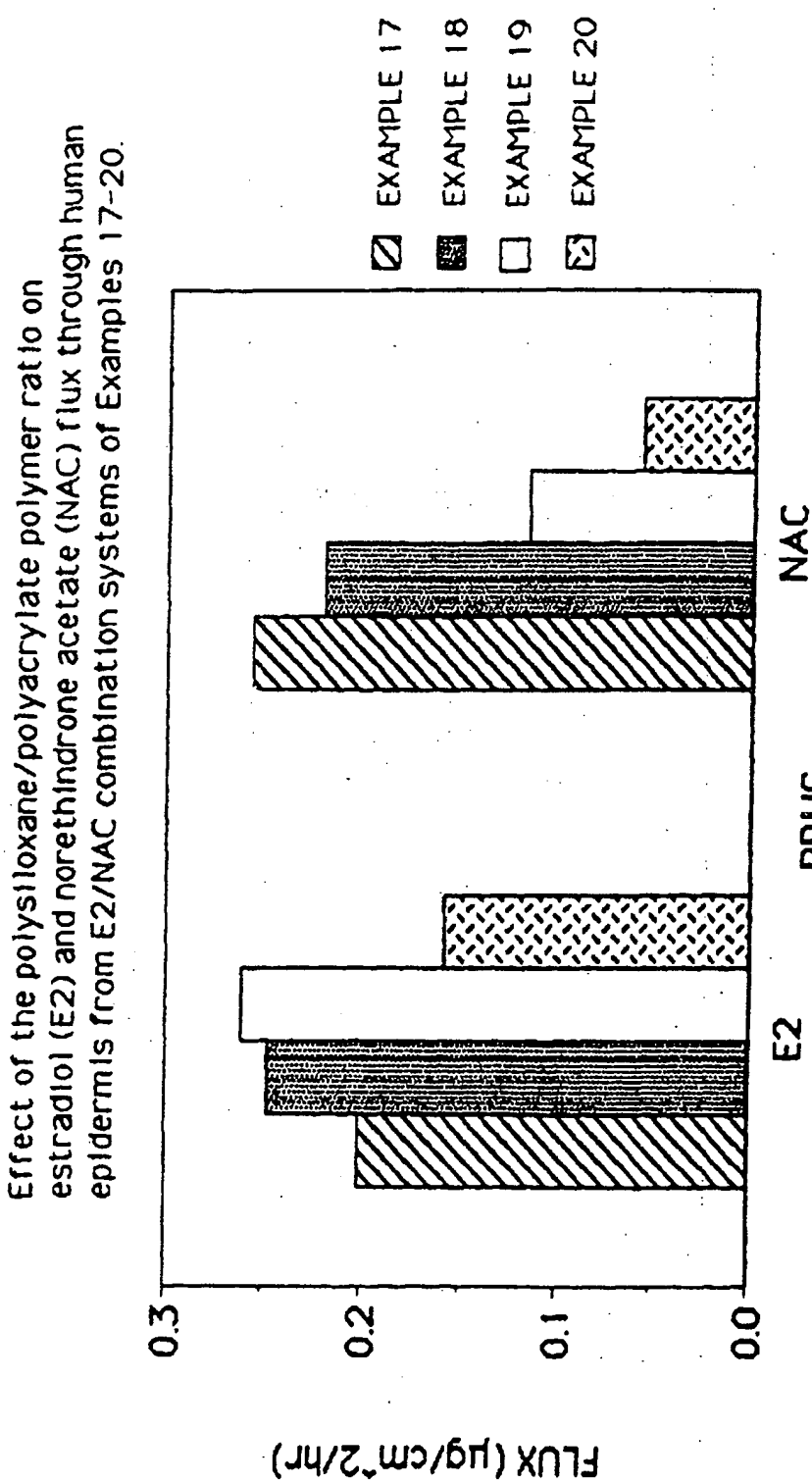
Effect of the polysiloxane/polyacrylate polymer ratio on estradiol (E2) and norethindrone acetate (NAC) flux through human epidermis from E2/NAC combination systems of Examples 17-20.
EXAMPLE 17
EXAMPLE 18
EXAMPLE 19
EXAMPLE 20
FLUX (μg/cm^2/hr)
0.3
0.2
0.1
0.0
E2
NAC
DRUG

FIG. 8

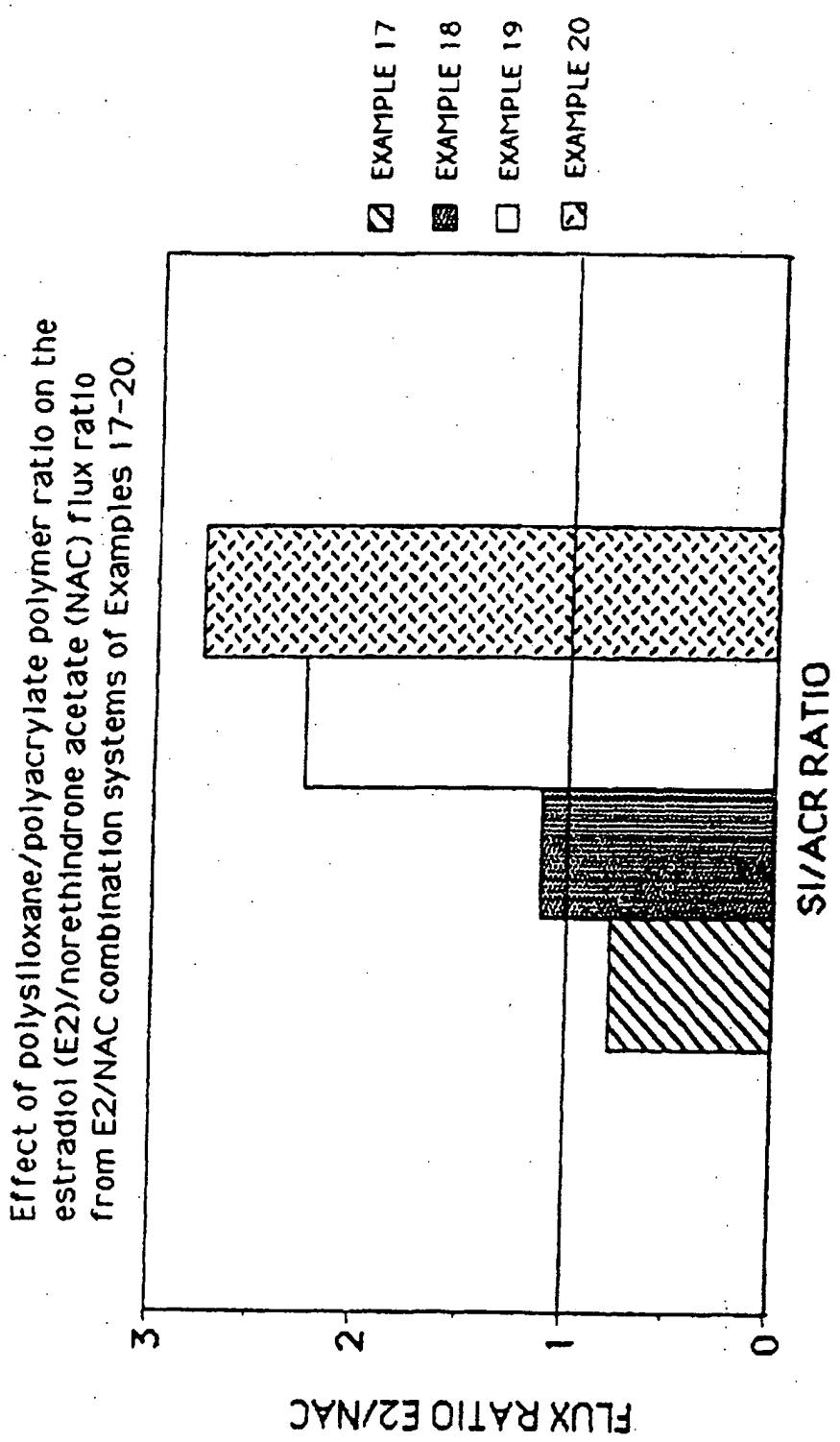
Effect of polysiloxane/polyacrylate polymer ratio on the estradiol (E2)/norethindrone acetate (NAC) flux ratio from E2/NAC combination systems of Examples 17-20.
EXAMPLE 17
EXAMPLE 18
EXAMPLE 19
EXAMPLE 20
FLUX RATIO E2/NAC
3
2
1
0
SI/ACR RATIO

FIG. 9

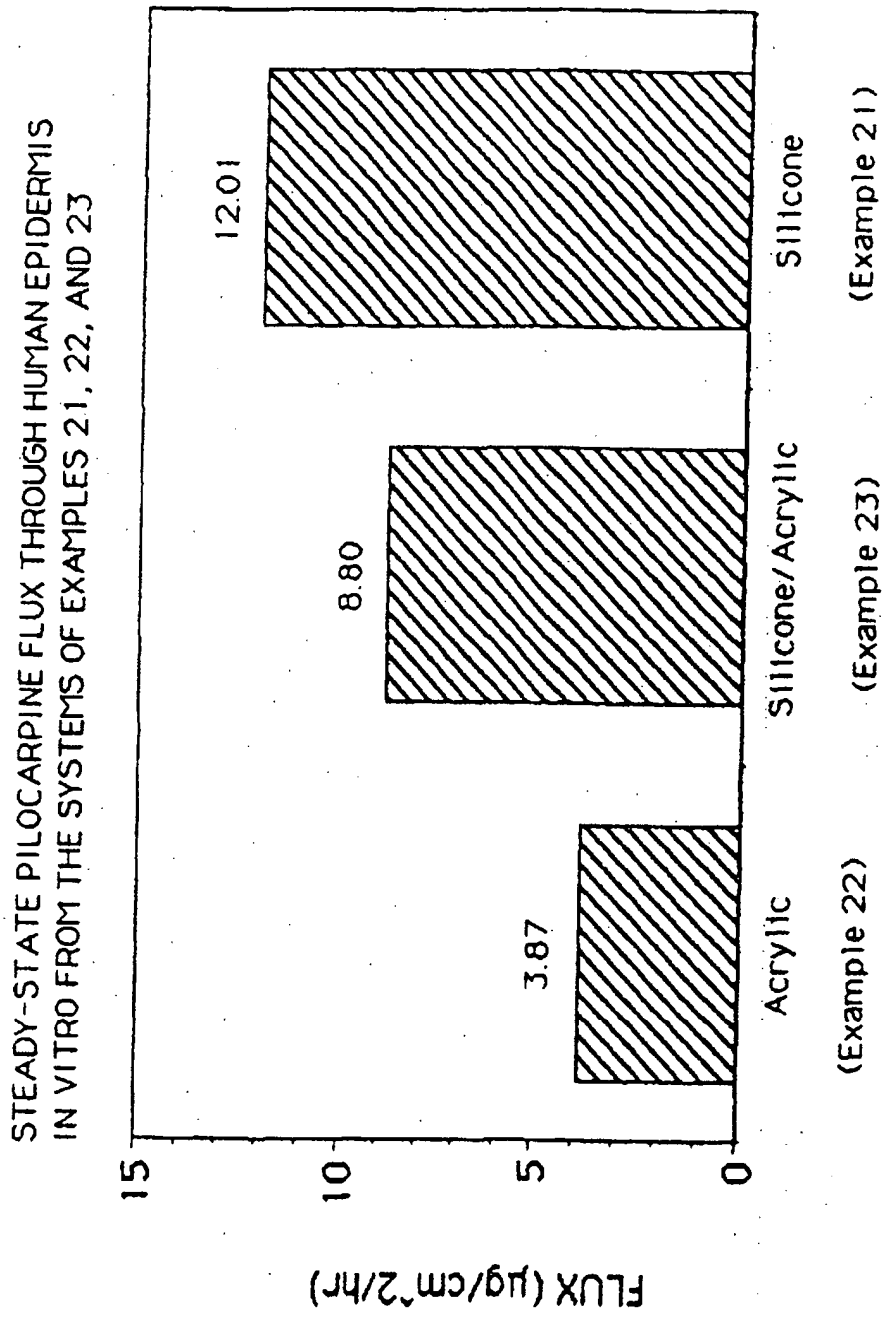
STEADY-STATE PILOCARPINE FLUX THROUGH HUMAN EPIDERMIS
IN VITRO FROM THE SYSTEMS OF EXAMPLES 21, 22, AND 23
FLUX (μg/cm^2/hr)
15
10
5
0
3.87
8.80
12.01
Acrylic
(Example 22)
Silicone/Acrylic
(Example 23)
Silicone
(Example 21)

FIG. 10

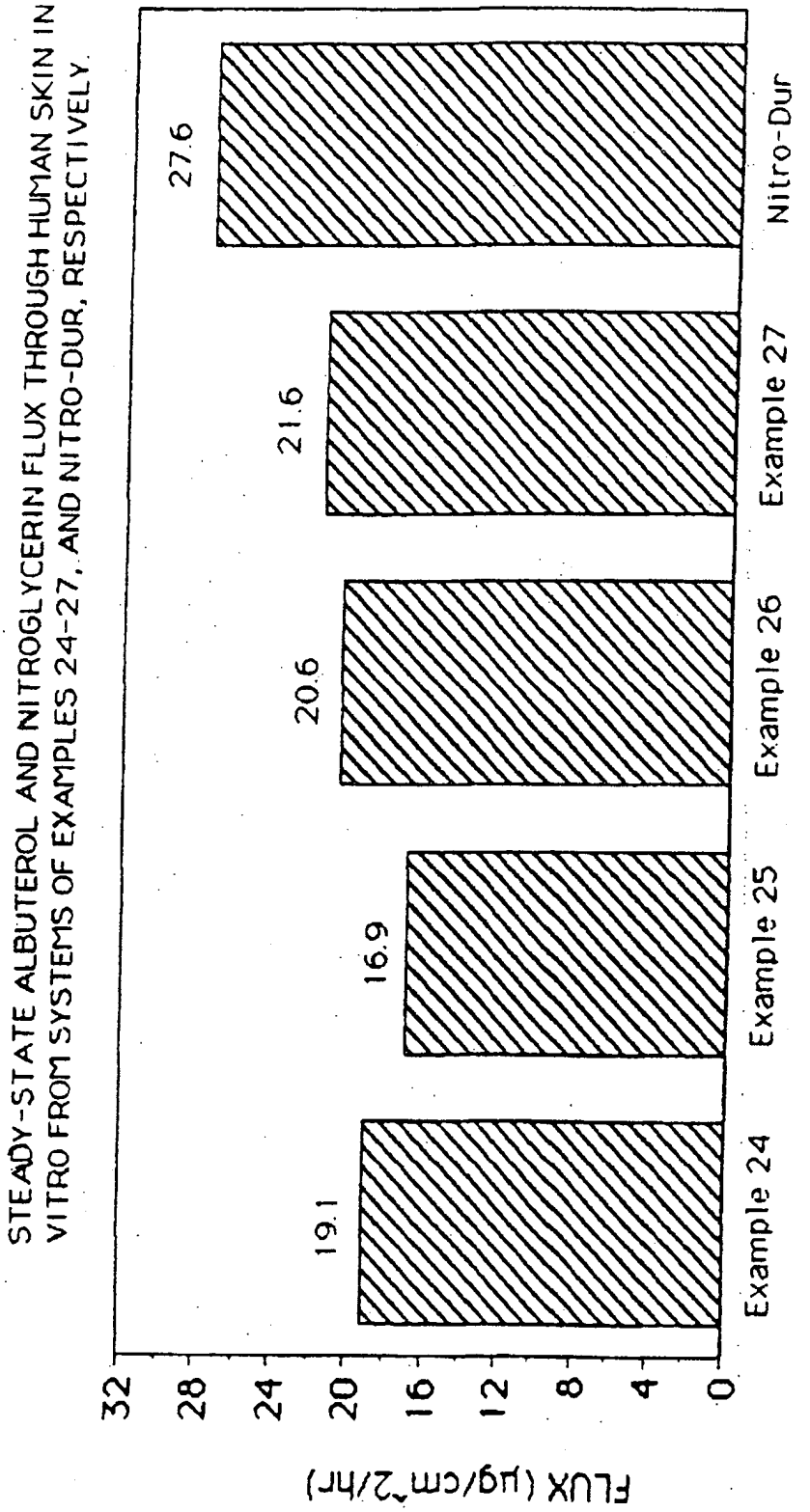
STEADY-STATE ALBUTEROL AND NITROGLYCERIN FLUX THROUGH HUMAN SKIN IN VITRO FROM SYSTEMS OF EXAMPLES 24-27, AND NITRO-DUR, RESPECTIVELY.
FLUX (μg/cm^2/hr)
0
4
8
12
16
20
24
28
32
19.1
16.9
20.6
21.6
27.6
Example 24
Example 25
Example 26
Example 27
Nitro-Dur
Composition

FIG. 11

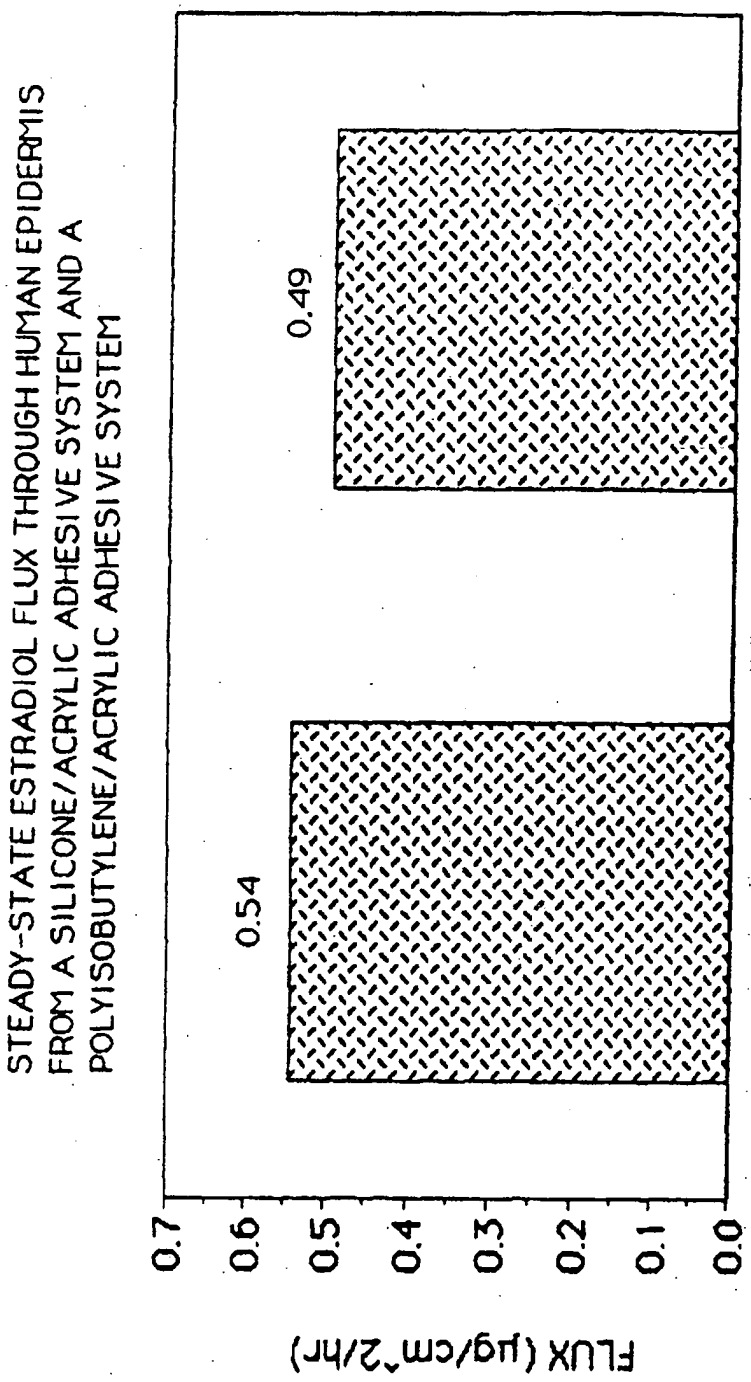
STEADY-STATE ESTRADIOL FLUX THROUGH HUMAN EPIDERMIS
FROM A SILICONE/ACRYLIC ADHESIVE SYSTEM AND A
POLYISOBUTYLENE/ACRYLIC ADHESIVE SYSTEM
FLUX (μg/cm^2/hr)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.54
0.49
Silicone/Acrylic
(EXAMPLE 29)
Polyisobutylene/Acrylic
(EXAMPLE 28)
ADHESIVE

FIG. 12

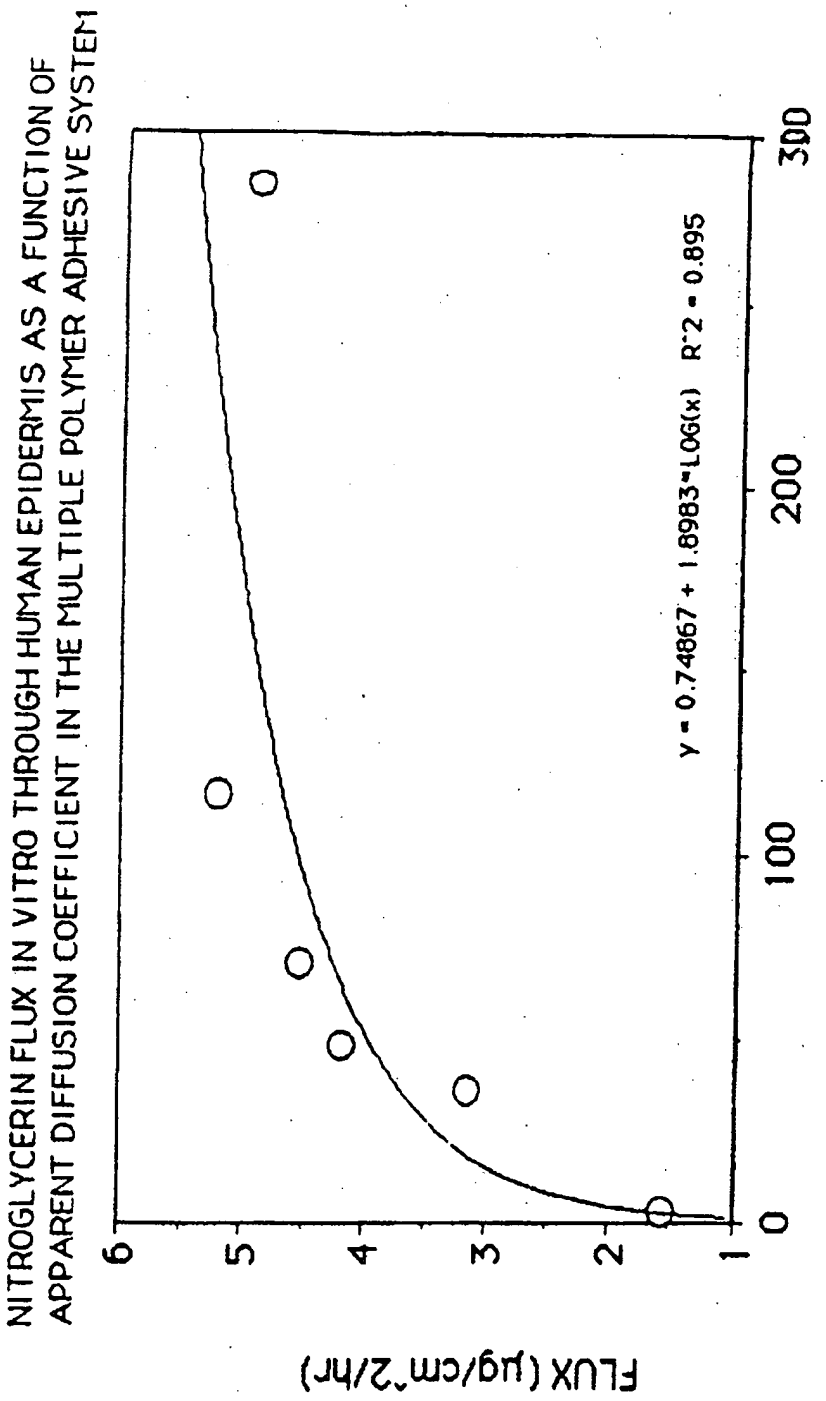
NITROGLYCERIN FLUX IN VITRO THROUGH HUMAN EPIDERMIS AS A FUNCTION OF APPARENT DIFFUSION COEFFICIENT IN THE MULTIPLE POLYMER ADHESIVE SYSTEM
FLUX (µg/cm^2/hr)
6
5
4
3
2
1
0
100
200
300
DIFFUSION COEFFICIENT (cm^2/sec)
Y = 0.74867 + 1.8983*LOG(x) R^2 = 0.895

FIG. 13

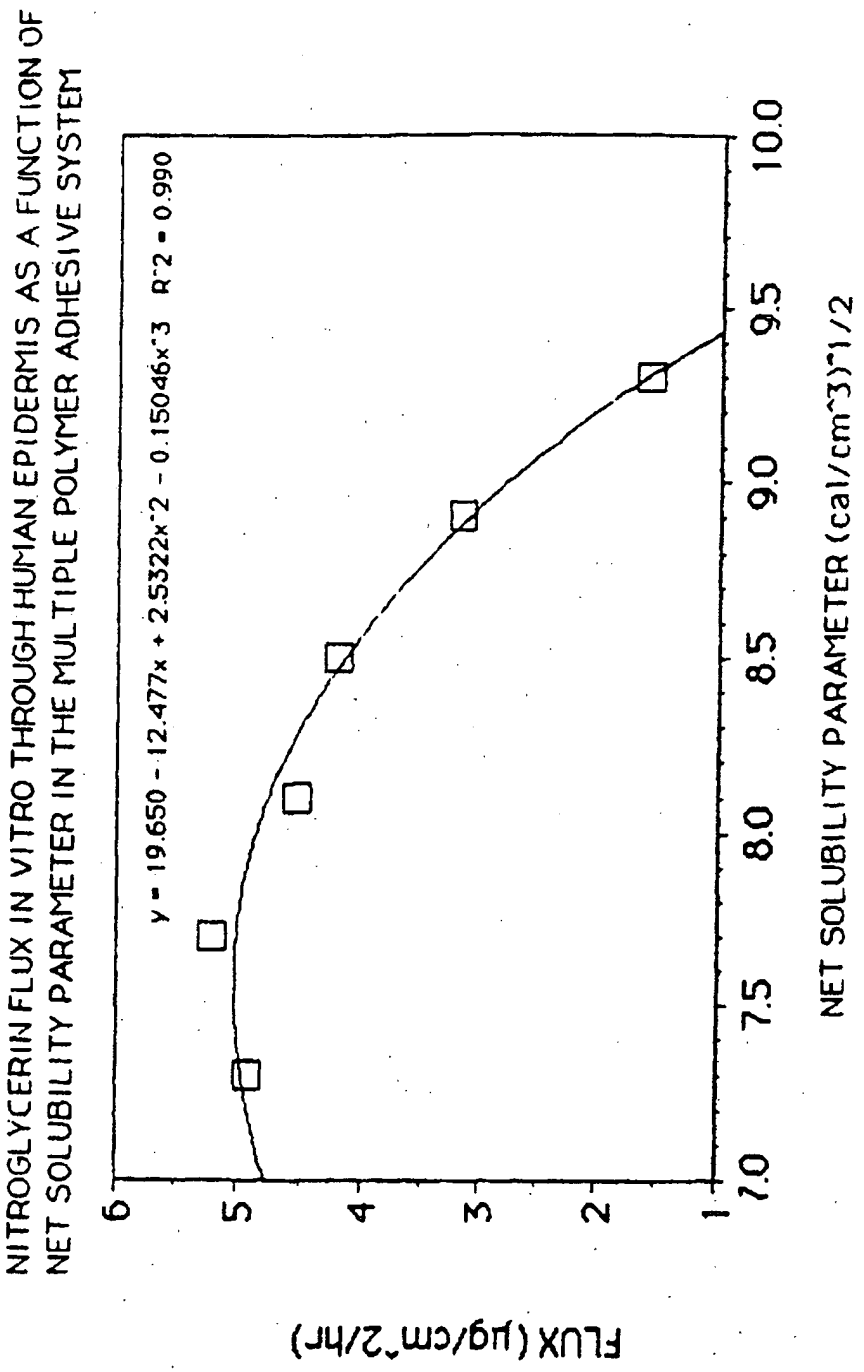
NITROGLYCERIN FLUX IN VITRO THROUGH HUMAN EPIDERMIS AS A FUNCTION OF NET SOLUBILITY PARAMETER IN THE MULTIPLE POLYMER ADHESIVE SYSTEM
y = 19.650 - 12.477x + 2.5322x^2 - 0.15046x^3 R^2 = 0.990
FLUX (µg/cm^2/hr)
6
5
4
3
2
1
7.0
7.5
8.0
8.5
9.0
9.5
10.0
NET SOLUBILITY PARAMETER (cal/cm^3)^1/2

FIG. 14

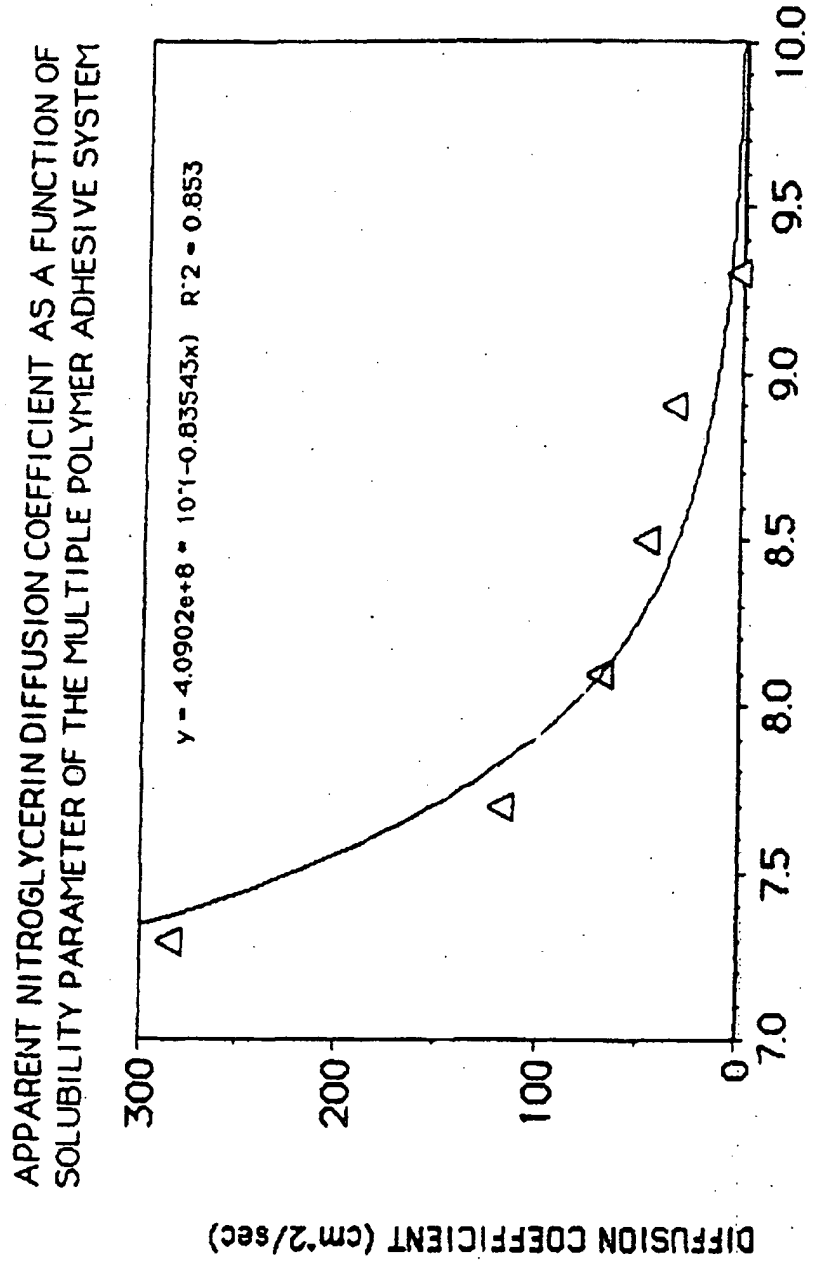
APPARENT NITROGLYCERIN DIFFUSION COEFFICIENT AS A FUNCTION OF SOLUBILITY PARAMETER OF THE MULTIPLE POLYMER ADHESIVE SYSTEM
y = 4.0902e+8 * 10^(-0.83543x) R^2 = 0.853
DIFFUSION COEFFICIENT (cm^2/sec)
300
200
100
0
7.0
7.5
8.0
8.5
9.0
9.5
10.0
SOLUBILITY PARAMETER (cal/cm^3)^1/2

FIG. 15